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British Journal of Obstetrics and Gynaecology

Edited by Frank E. Hytten

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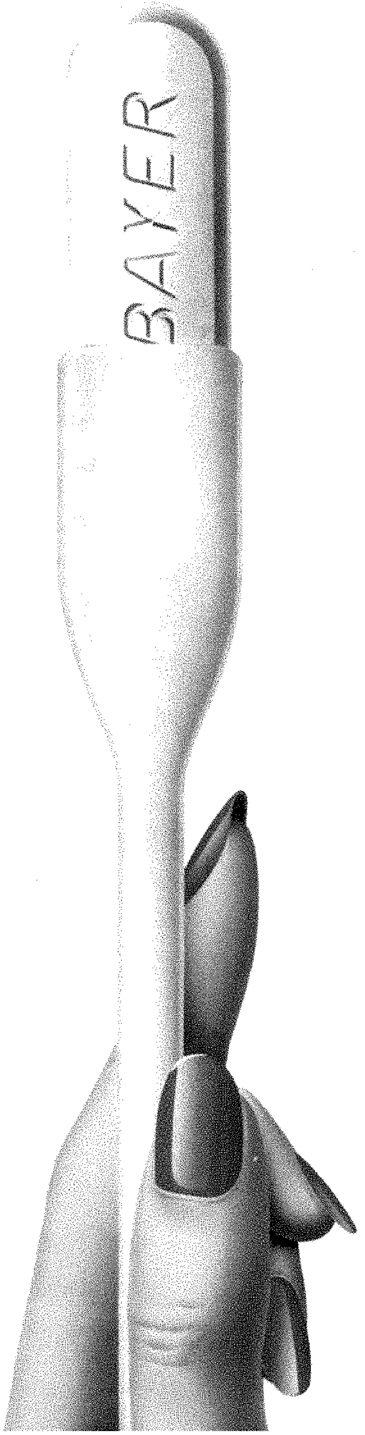

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Reference 1. Ritter, W., Pharmacokinetic fundamentals of vaginal treatment with clotrimazole. *Am. J. Obstet. Gynecol.* 1985; 152(7) [Part 2]: 945-7.

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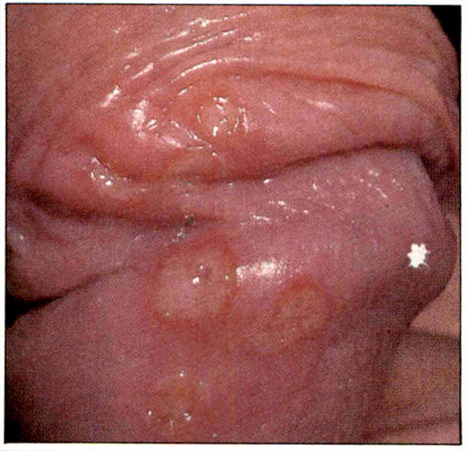

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3. Chen.J.K. & Elder,M.G., *Obstet.Gynecol.*, 1983, **62,** 339.
ristensen,N.J., Bygdeman,M. & Green,K., *Contraception*, 1983,
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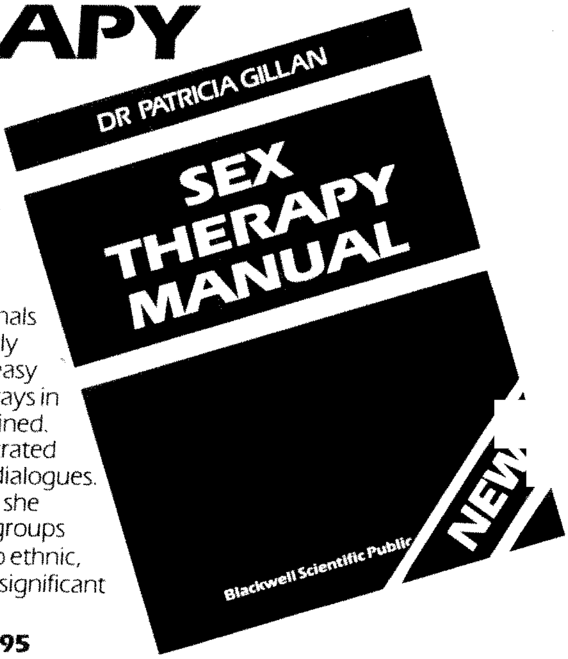

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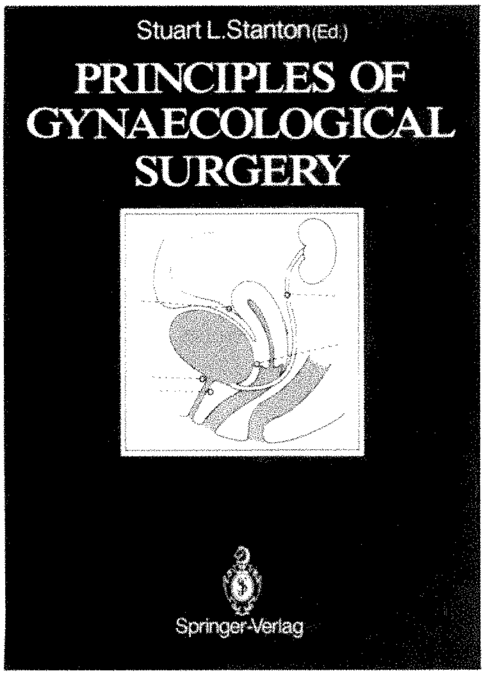

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1987. 152 figures. XII, 306 pages.
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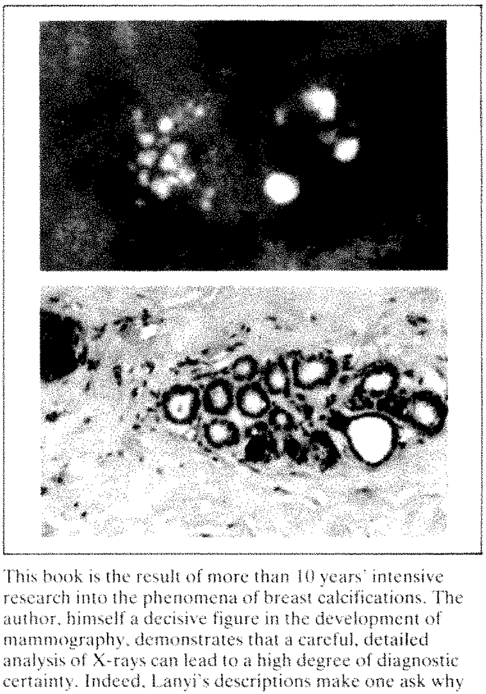

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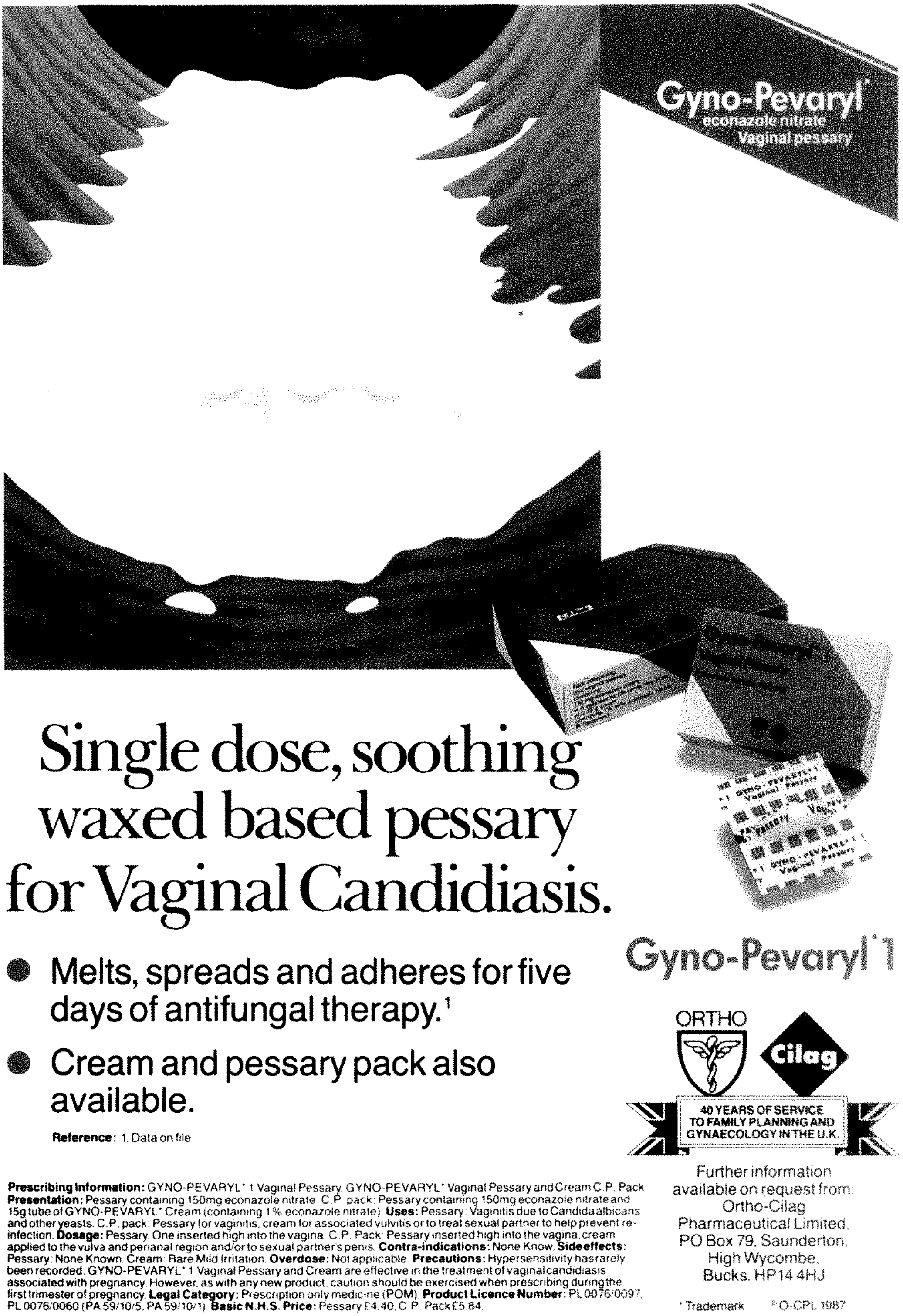

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The Intrauterine Life - Management and Therapy

Proceedings of the 2nd International Symposium on The Fetus as a Patient, Diagnosis and Treatment, Jerusalem, Israel, May 26-31, 1985

edited by **J. G. Schenker** *and* **D. Weinstein**

(International Congress Series No. 689)

1986 496 pages
Price: US $ 111.00/Dfl. 250.00
ISBN 0-444-80806-x

The book contains selected papers on the physiological and pathophysiological conditions of the fetus, its assessment and therapy which were presented at the Second International Meeting "The Fetus as a Patient", held in Jerusalem in May 1985. Approximately 450 scientists and clinicians from 29 countries gathered in the Holy City of Jerusalem to present and discuss the results of their investigations and their clinical experiences in this new field of obstetrics.

The book opens with a section on the ethical, legal and religious aspects of modern diagnostic and reproductive approaches to the fetus. Further chapters cover the following subjects: perinatal care, assessment of fetal well being by biochemical and biophysical techniques, maternal medical complications affecting the fetus, diagnosis and management of fetal malformation.

It is our hope this book will help disseminate the vast data and experience expressed by its scholarly participants, and thereby aid to define the present state of knowledge in fetal medicine.

Perinatal Care and Gestosis

Proceedings on the 17th Meeting of Organisation Gestosis, International Symposium on Perinatal Care and Gestosis, Sendai, Japan, 17-22 May 1985

edited by **M. Suzuki**

(International Congress Series No. 686)

1985 536 pages
Price: US $ 122.25/Dfl. 275.00
ISBN 0-444-80736-5

This book is divided into three sections: Special Lectures, Symposia and Free Communications.
The first section centers around pregnancy induced hypertension, its relationship and effects with regard to; perinatal mortality, smooth muscle contraction, malnutrition and stress, uterine resting tonus and magnesium sulfate therapy. A chapter also deals with the history and expected progress in EPH gestosis.
Symposia (the second section), has as its predominant theme, fetal and fetoplacental bloodflow, and two chapters deal with the systems of measurement used.
In addition, a chapter deals with prostaglandins in pregnancy, while other chapters deal with topics such as eclampsia, prolactin in gestosis, and endocrinological aspects of gestosis. This section ends with a chapter entitled 'Immunology in a possible etiology of renal lesion in gestosis'.
An extensive 'Free Communication' section gives in a broad approach clinical evaluations, drugs used and their roles, therapies, analysis and ongoing studies in this many-sided field.

Recent Advances in Ultrasound Diagnosis 5

Proceedings of the International Symposium, Dubrovnik, 29-30 Sept. 1985

edited by **A. Kurjak** *and* **G. Kossoff**

(International Congress Series No. 701)

1986 232 pages
Price: US $ 80.00/Dfl. 180.00
ISBN 0-444-80889-6

Interventional ultrasound and measurements of human blood flow are two specific topics discussed in Recent Advances in Ultrasound Diagnosis 5, in addition to general aspects of the significant advances in diagnostic ultrasound. The new technique of the ultrasonically guided puncture, invaluable for a variety of therapeutic purposes, has been discussed by a number of experts, including H. H. Holm, a pioneer and top expert in the field. Chapters dealing with the field of ultrasonic measurements of human blood flow in the fetal aorta, umbilical vessels, uterine arteries and ovarian vessels, as well as the new colour Doppler technique are presented.

Neonatal therapy: an update

Proceedings of the International Symposium, Padova 13-14 September 1985

edited by **F. F. Rubaltelli** *and* **B. Granati**

(International Congress Series No. 723)

1985 316 pages
Price: US $ 100.00/Dfl. 225.00
ISBN 0-444-80809-4

The past decade has brought a mass of new therapeutic practices to the attention of the neonatologist. Most of the contributors to this book are pioneers in their fields, each of whom recognized the need for an improved understanding of the basis of neonatal therapy. The aim of the authors is to discuss the current state of knowledge of the more important areas of treatment of sick preterm and fullterm newborns. The subject matter is not confined to a review of antimicrobial and antiviral agents, but is concerned with other very important aspects of the care which must be given to the sick newborn, such as for example, nutrition, respiratory support, phototherapy, cardiovascular drugs, and diuretics. This authoritative volume offers a unique resource for neonatologists and pediatricians responsible for the treatment of illnesses of the newborn.

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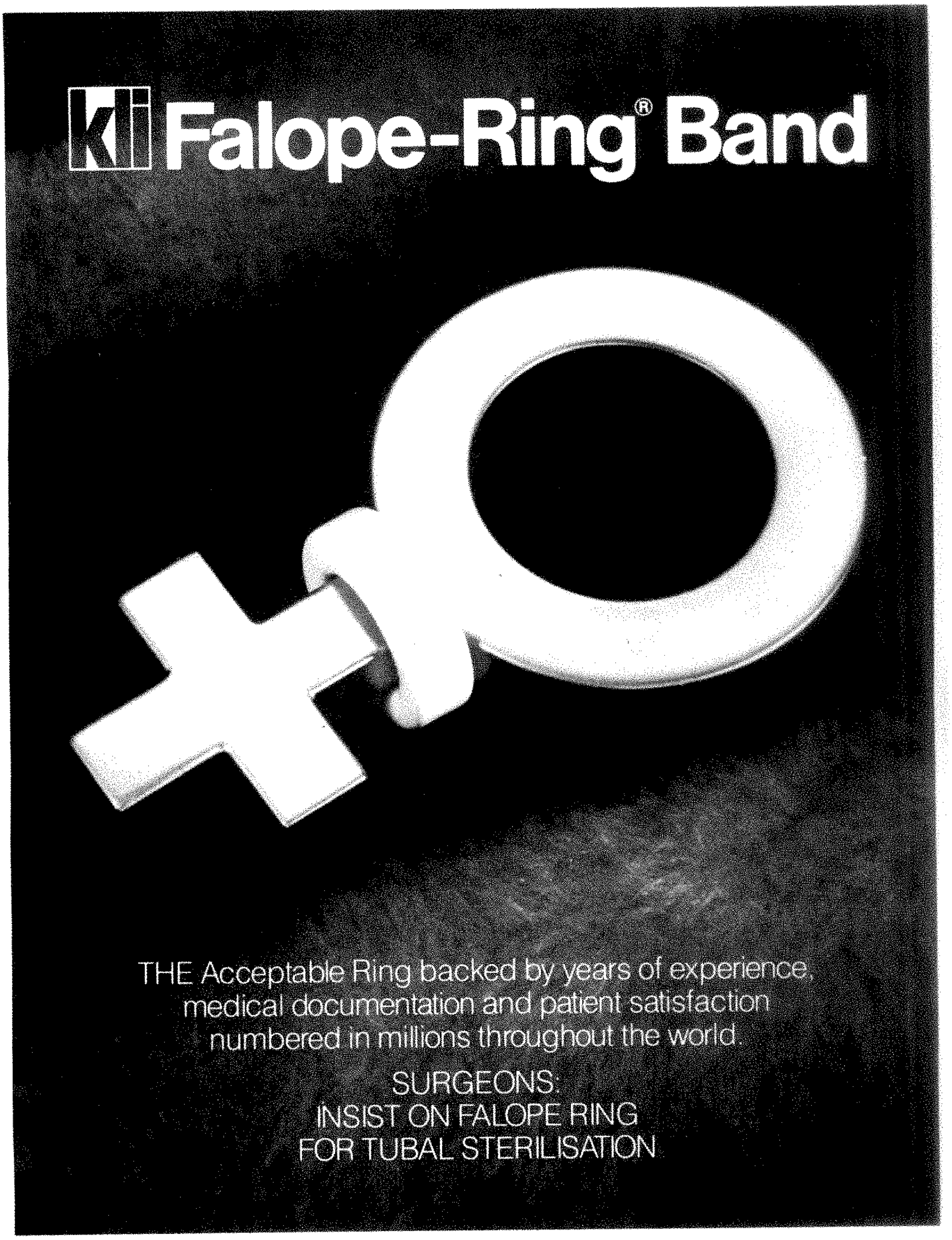
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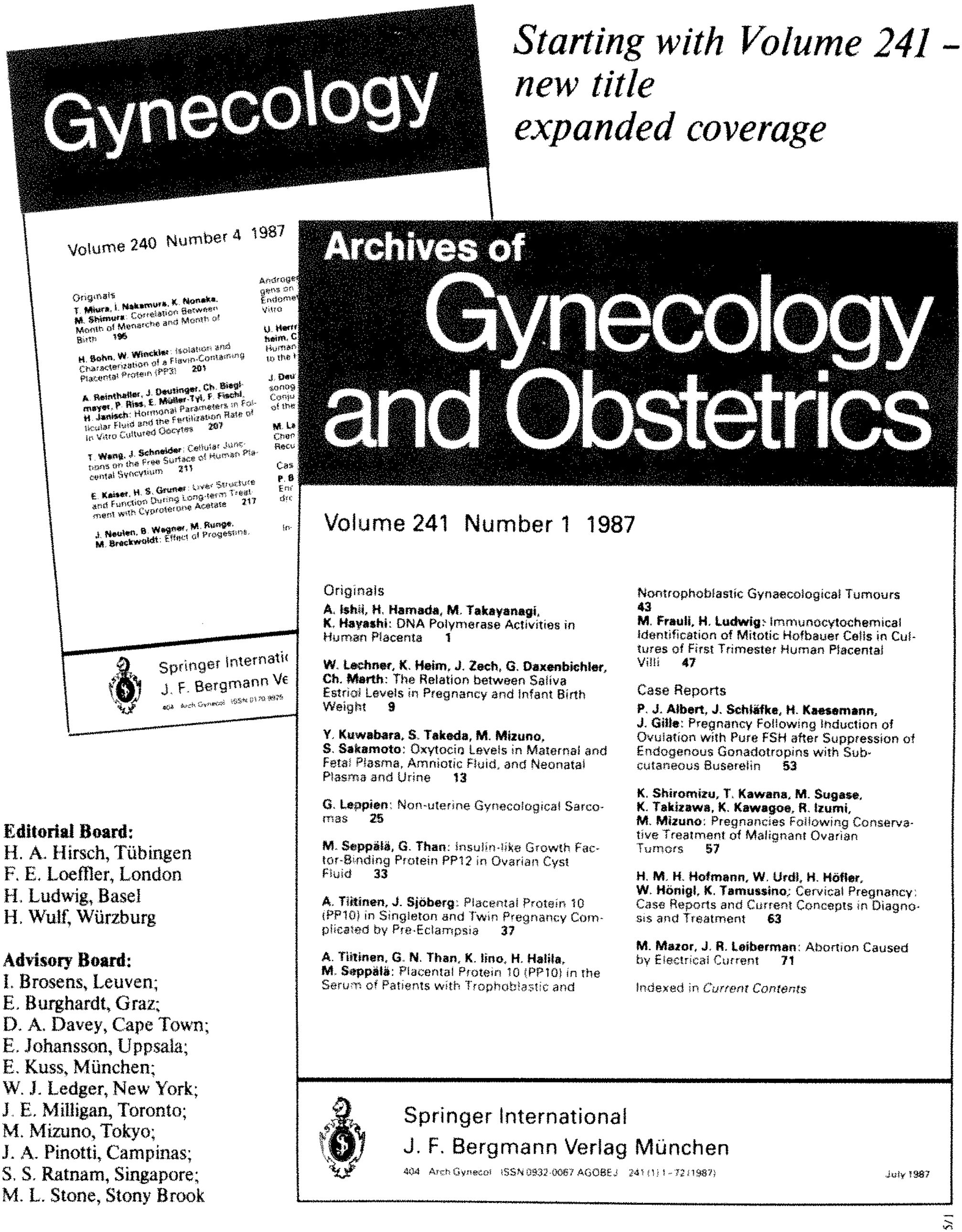

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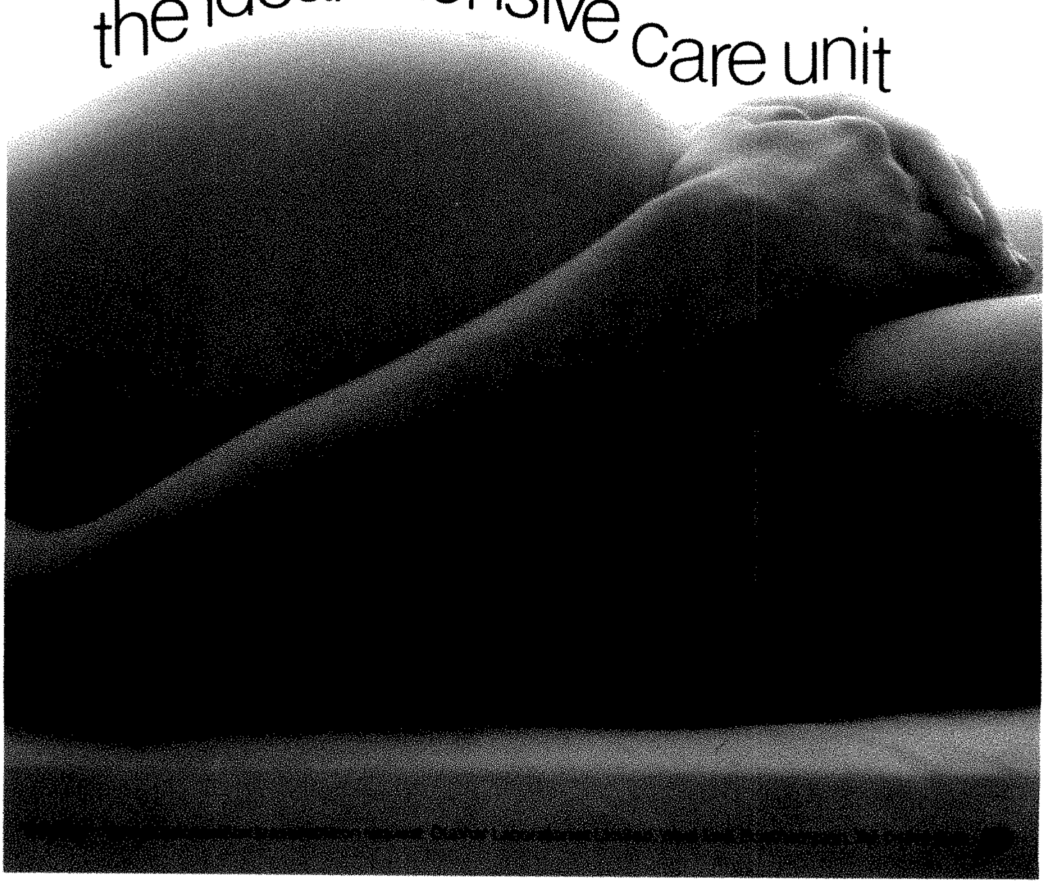
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COMMENTARY

Combining results from several clinical trials

In many research areas several clinical trials have been carried out independently to compare the same or closely similar treatments. Inevitably the different trials will vary in the magnitude, and sometimes even in the direction of the observed treatment effect, especially if the trials are small. There will usually also be inconsistency regarding statistical significance. However, many clinical trials are much too small to detect modest, but clinically important, treatment effects, so it cannot be assumed that two treatments are equally effective simply because few, if any, clinical trials have found a statistically significant difference. Further, the quality of published trials varies, with clear implications for the reliability of their results.

Over the last decade or so the use of statistical methods for the analysis of the results of multiple clinical studies has become more common. The approach is known either as a *meta-analysis* or an *overview*, of which two examples appear in this issue of the Journal (Elbourne *et al.* 1988; Prendiville *et al.* 1988).

There are three key steps in a meta-analysis: (a) identify all the relevant trials (preferably including unpublished studies); (b) assess their methodological quality; and (c) synthesize the results to get an overall assessment of the comparative efficacy of the treatments. It is essential to specify in advance the methods to be used at each stage

Identification of all trials

There is considerable scope for bias in the selection of studies to review (Gøtzsche 1987). Ideally a review of a topic should include the results of all clinical trials carried out, whether or not the results have been published. Although computerized databases are enormously valuable for locating most published studies, many references will be missed (Dickersin *et al.* 1985), so it is also necessary to carry out a more exhaustive search for published trials (Sacks *et al.* 1987). The issue of unpublished studies is more problematic. There is increasing evidence of publication bias, whereby clinical trials are more likely to be published if they report a statistically significant difference between treatments. However, obtaining information on unpublished trials is both difficult and time-consuming, and while it is undoubtedly desirable to include such information, in many circumstances it is not feasible A reasonably objective appraisal of all the published evidence, even if there may be some publication bias, is still valuable.

Quality assessment

An overview must include at least an assessment of the extent of three potential sources of bias—selection bias at trial entry, selection bias after trial entry, and measurement bias (Prendiville *et al.* 1988). There are, however, some much more complex assessment schemes (Chalmers *et al.* 1981). The assessment should preferably be carried out independently by at least two people.

The assessment is necessarily limited by the information available, usually in the Methods section of the paper but sometimes discernible from elsewhere within a paper or perhaps directly from the authors. It can be used to select which studies should be excluded from a meta-analysis. For example, many overviews are based only on randomized controlled trials. The quality assessments can also be used by readers to aid their interpretation of the review, to rank studies in order of methodological quality (as in the two papers in this issue), or even to assign numerical weightings to the results of different studies.

Combining results

In general, the endpoint of clinical trials is a binary variable, such as died/alive or cured/not cured. Meta-analysis of clinical trials is usually performed by a Mantel–Haenszel analysis, preferably in combination with a graphical display of estimated odds ratios and confidence intervals for each trial (DeMets 1987). The graphical display gives a visual indication of the consistency of the findings and also the uncertainty attached to the results of each trial. The trials with the wider confidence intervals have the least reliable results as a consequence of their small sample size.

The basic principle of the method is to calculate an estimate of the difference between the effects of the two treatments for each trial and then to construct a weighted combination of the estimates, the weights depending on the variance of each difference. The actual data for the separate studies are not combined. The analysis leads to an estimate of the 'typical' relative treatment effect, in the form of an odds ratio. The confidence interval for this estimate is much narrower than that for individual trials. The odds ratio is an approximation to the relative risk associated with the specified outcome in the two treatment groups. An odds ratio of around 1·0 indicates equal risk in both groups, while an odds ratio of 2·0 (or 0·5) indicates that one treatment has twice the risk of the other.

Interpretation

Although the statistical analysis of the results of several trials is fairly straightforward, meta-analysis should not be seen as an automated procedure. An important part of a meta-analysis is the tabulation of the characteristics and results of the individual trials.

The trials are bound to vary, for example in the type of subjects studied or the precise nature of the intervention. The extent to which it is reasonable to combine trials with different characteristics must be a matter of judgment.

A meta-analysis of a group of trials which differ to some extent still gives valuable information of the average effect observed over those trials. Nevertheless, the detailed description of all the trials allows the reader to re-analyse the data with alternative criteria for including trials, or to examine subsets of trials.

With statistical overviews, readers must be cautious about placing undue reliance on the estimated 'typical' effect. *Any* review of existing research findings is limited by the quantity and quality of information available. While an overview may answer some broader questions, it may also suggest areas for further research. In general, in order to answer more detailed questions about treatment benefits there can be no substitute for the well-designed, well-conducted clinical trial of adequate size.

Douglas G. Altman
Section of Medical Statistics
Clinical Research Centre
Watford Road
Harrow
Middlesex HA1 3UJ
Diana Elbourne
National Perinatal Epidemiology Unit
Radcliffe Infirmary
Oxford OX2 6HE

References

Chalmers, T C., Smith, H., Blackburn, B., Silverman, B , Schroeder, B., Reitman, D. & Ambroz, A. (1981) A method for assessing the quality of a randomized clinical trial. *Controlled Clin Trials* **2,** 31-49

DeMets, D. L. (1987) Methods for combining randomized clinical trials· strengths and limitations. *Stat Med* **6,** 341-348.

Dickersin, K., Hewitt, P., Mutch, L., Chalmers, I. & Chalmers, T. C. (1985) Persuing the literature: comparison of MEDLINE searching with a perinatal trials database. *Controlled Clin Trials* **6,** 168-177

Elbourne, D., Prendiville, W. & Chalmers, I. (1988) Choice of oxytocic preparation for routine use in the management of the third stage of labour. *Br J Obstet Gynaecol* **95,** 17-30.

Gøtzsche, P. C. (1987) Reference bias in reports of drug trials. *Br Med J* **295,** 654-656.

Prendiville, W , Elbourne, D. & Chalmers, I. (1988) The effects of routine oxytocic administration in the management of the third stage of labour: an overview of the evidence from controlled trials. *Br J Obstet Gynaecol* **95,** 3-16.

Sacks, H. S., Berner, J., Reitman, D., Ancona-Berk, V. A. & Chalmers, T C. (1987) Meta-analyses of randomized controlled trials *New Engl J Med* **316,** 450-455.

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The effects of routine oxytocic administration in the management of the third stage of labour: an overview of the evidence from controlled trials

WALTER PRENDIVILLE, DIANA ELBOURNE, IAIN CHALMERS

Summary. Recent claims that routine active management of the third stage of labour increases rather than decreases maternal and neonatal morbidity have prompted us to conduct a systematic review of the relevant controlled trials. In this paper we have analysed data derived from a total of nine published reports of controlled trials in which an oxytocic drug was compared with either a placebo or no routine prophylactic. Oxytocic drugs used routinely appear to reduce the risk of postpartum haemorrhage by about 40% (typical odds ratio 0·57, 95% confidence interval 0·44–0·73) implying that for every 22 women given such an oxytocic, one postpartum haemorrhage could be prevented. The available data are insufficient to assess the possible effects of this policy on the incidence of retained placenta, hypertension and other possible adverse effects.

The introduction of oxytocic drugs for the treatment of postpartum haemorrhage has been regarded as 'one of the enduring achievements of modern science' (Moir 1964). In the 1940s haemorrhage was the commonest cause of maternal mortality in the UK (Gilliat 1949) and in the USA (Greenhill 1951). Mortality rates varied from 1 in 1318 in Canada (Conn, Vant & Cantor 1941) to 1 in approximately 5000 in the UK (Martin & Dumoulin 1935).

Against this background obstetricians welcomed the introduction of a drug that promised to prevent a number of these deaths. It was the pioneering work of Moir (1932) which led to the discovery that ergometrine was the active principle on which the traditional oxytocic effect of ergot had depended (Dudley & Moir 1935), and after the introduction of ergometrine into obstetric practice half a century ago this particular oxytocic drug became widely accepted as a means of controlling postpartum haemorrhage. Reviewing the use of ergometrine in obstetric practice, Moir (1955) wrote 'Few drugs can have become so firmly established in so short a time and few drugs can be so completely indispensable as ergometrine now is'. He described a fall in the death rate from postpartum haemorrhage coincident with the introduction of the use of oxytocics to UK obstetric practice, but he acknowledged the possible confounding influence of such factors as the widespread introduction of blood transfusion services and the advent of sulphonamides and penicillin (Moir 1955). This period was also a time of quite dramatic socio-economic changes, and the improved nutritional status of women and the antenatal care they received may have contributed to the reduced reported incidence of postpartum haemorrhage. Nevertheless, the maternal death

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Department of Obstetrics and Gynaecology, Bristol Maternity Hospital, Southwell Street, Bristol BS2 8EG
WALTER PRENDIVILLE *Lecturer*

National Perinatal Epidemiology Unit, Radcliffe Infirmary, Oxford OX2 6HE
DIANA ELBOURNE *Social Statistician*
IAIN CHALMERS *Director*

Correspondence: Walter Prendiville

rate from postpartum haemorrhage fell from its previously static level of approximately 0·3/1000 births throughout the 1930s to 0·06/1000 births in 1952. Few would dispute the role that oxytocic drugs must have played in managing postpartum haemorrhage effectively.

By contrast, the *routine* administration of oxytocic drugs in an attempt to *prevent* postpartum haemorrhage has not been accepted universally as an obstetric policy. During the 1940s several papers claimed a beneficial effect of routine administration of ergometrine in managing the third stage of labour (see review by Dumoulin 1981). At this time the use of prophylactic oxytocic administration in the form of ergometrine (ergonovine in the USA) appeared to be popular in the USA (Martin & Dumoulin 1953) but was accepted less enthusiastically in the UK. Indeed, the practice was roundly condemned by Kerr & Moir (1949).

Du Vigneaud (1953) reported the synthesis of oxytocin and subsequently Embrey *et al.* (1963) reported the advantages of combining this with ergometrine—as Syntometrine, the value of which was claimed to lie in the rapid effect of the oxytocin and the sustained effect of ergometrine (Embrey *et al.* 1963). A few years after the introduction of Syntometrine in the UK it became routine practice to administer this combined preparation prophylactically, usually in association with controlled cord traction to deliver the placenta (Kimbell 1958; Spencer 1962). In the UK and elsewhere it has now become standard teaching to advocate routine oxytocic administration for managing the third stage of labour (Fleigner & Hibbard 1966; Hibbard 1964; Llewellyn Jones 1986; Myles 1985; Beischer & Mackay 1986; Turnbull 1976; Hickman 1978; Bender & Tindall 1980; Clayton *et al.* 1980; Marsh 1985).

This teaching is reflected in the results of a survey of policies for the care of normal women in consultant and general practitioner (GP) maternity units in England in 1984 (Garcia *et al.* 1987) which showed that an active management policy with Syntometrine and controlled cord traction was universal in those units which are known to have had a policy for third stage management. Only two out of 238 consultant units reported that one or more consultant obstetricians used oxytocin rather than Syntometrine routinely. A few other GP and consultant units reported that they offered women a choice about third stage management in their discussions of a birth plan. Some other units reported that their policy was to use active management except when women requested otherwise.

Some women using the maternity services have begun to challenge the routine use of oxytocics for managing the third stage of labour (Chamberlain 1985; Milton 1985), not only because obstetric routines have come under general attack from many quarters, but also because the scientific basis of a policy of prophylactic oxytocic administration, usually as part of the active management of the third stage of labour, has been challenged. Dunn, a British paediatrician, has for many years pointed to evidence that these obstetric practices may interfere with physiological processes to the detriment of both mother and baby (Dunn 1966*a*, *b*, 1973, 1985; Dunn *et al.* 1966). More recently, Inch (1985) has offered evidence to support the view that routine active management of the third stage of labour promotes a 'cascade of intervention' through which controlled cord traction becomes necessary because (i) women are delivered of the placenta without the aid of gravity, (ii) the umbilical cord is clamped early and routinely, and (iii) a prophylactic oxytocic has been administered.

These uncertainties about the scientific basis of the current management of the third stage of labour have prompted us to conduct a review of currently available evidence, and to mount new research to address questions which cannot be answered with these data. The analysis presented in this report addresses one main question: is there strong scientific evidence to support the routine use of oxytocic drugs to prevent postpartum haemorrhage?

We have addressed this question by analysing data derived from prospective controlled trials in which a policy of routinely administering oxytocics prophylactically to reduce the risk of postpartum haemorrhage has been compared with either a placebo group or a group in which oxytocics were only used selectively Specifically, we tested the hypothesis that routine use of oxytocic drugs reduces the incidence of postpartum haemorrhage (blood loss >500 ml). We also attempted to assess whether routine use of oxytocics reduces the need for (further) oxytocic administration and increases the incidence of retained placenta and manual removal of the placenta. Although the hypertensive effect of ergometrine has been frequently reported

(Hamilton *et al.* 1952; Baillie 1963; Hendricks & Brenner 1970; Johnstone 1972; Moir & Amoa 1979; Dumoulin 1981), we have also tried to use data from the trials to estimate the extent to which routine use of oxytocic drugs increases the risk of hypertension. Preliminary scrutiny of the available reports suggested that there would be inadequate data to permit assessment of hypotheses concerning possible adverse effects on the newborn.

Materials and methods

Identification and selection of relevant studies

We have attempted to locate all published reports of controlled trials of oxytocics for the management of the third stage of labour using the Oxford Database of Perinatal Trials (National Perinatal Epidemiology Unit 1985). Reports are entered onto the database if the intervention being assessed has occurred during pregnancy or within 28 days of delivery, and the allocation of the intervention(s) has been decided either by formal randomization or by some other 'quasi-random' method such as alternation. Further details of the database and the completeness of its coverage of perinatal trials are available elsewhere (Dickersin *et al.* 1985; Chalmers *et al.* 1986).

Our search of the database yielded 27 reports of controlled trials of oxytocics used in the management of the third stage of labour. Eighteen of these were excluded from this analysis as they did not use a concurrent, non-oxytocic comparison group (Moore 1956; Forster 1957; Fugo & Dieckmann 1958; Groeber & Bishop 1960; Barbaro & Smith 1961; Chukudebelu *et al.* 1963; Nieminen & Jarvinen 1963; Stearn 1963; Bonham 1963; Soiva & Koistinen 1964; Francis *et al.* 1965 (one paper reporting two trials); Paull & Ratten 1977; Sorbe 1978; Docherty & Hooper 1981; Dumoulin 1981; Nelson 1983; Symes 1984). Nine reports remained for further analysis (Daley 1951; McGinty 1956; Friedman 1957; Newton *et al.* 1961; Howard *et al.* 1964; Vaughan Williams *et al.* 1974; Hacker & Biggs 1979; Kerekes & Domokos 1979; Rooney *et al.* 1985).

As shown in Table 1, the reports were published over a span of 34 years (between 1951 and 1985). Overall, the trials included 4494 women of whom 1599 had been allocated to a 'no oxytocic' control group. The sample sizes of individual trials ranged from 26 to 1459 women. The criteria for trial entry varied considerably between the studies, as did the drugs studied and their route of administration.

The oxytocic drugs assessed can be broadly divided into four categories: (i) ergot alkaloids including ergometrine/ergonovine (7 groups of women), methergine (3 groups), and dihydroergotamine methanesulfonate (DHE) (1 group); (ii) oxytocins including oxytocin (2 groups), Syntocinon (1 group), and Pitocin (2 groups); (iii) prostaglandins ($PGF_2\alpha$) (1 group); and (iv) Syntometrine comprising 5 i.u. Syntocinon and 0·5 mg ergometrine (4 groups). Eight of the active drugs were given intramuscularly, 9 intravenously, 3 either intramuscularly or intravenously, and 1 intramyometrially. The timing of drug administration ranged from crowning of the head (1), through to the birth of the anterior shoulder (8), after delivery of the baby (1), after cord clamping (2), and after delivery of the placenta (7), to 20 min after delivery (2). In all but one study the principal outcome of interest was blood loss, variously defined.

In this paper, comparisons have been made between all actively treated groups combined, and untreated controls. In an accompanying paper (Elbourne *et al.* 1988) we have compared different oxytocic drugs.

Attempts to obtain missing data

Although there are unlikely to be many, if any, relevant but unidentified published reports (Dickersin *et al.* 1985), other relevant trials may have been conducted but not published For obvious reasons we cannot assess the extent to which the trials which have been published represent a biased sample of all trials conducted

We tried to overcome two other potential sources of bias: (a) failure to publish primary analyses based on *all* cases allocated, and (b) selective reporting of data on the outcomes in which we were interested. We sent the authors of all nine reports incomplete tabulations of 'raw data' derived from the published reports, requesting that the missing data should be added in the empty cells in the tabulations. After conducting our analyses on all the available data, we sent copies of our draft manuscript to the authors, both for comment and in the continued hope that this would prompt answers to our queries and lead to the provision of additional

Table 1. Clinical characteristics of the studies

Study					Sample size				
No.	Author	Entry criteria	Drug	Route	Oxytocic	Control	Timing	Third stage management	Outcome data
1	Daley (1951)	Labour <48 h; parity <5; spontaneous vertex delivery, singletons, no APH, hydramnios or traumatic haemorrhage	Ergometrine (0·5 mg)	i.m into thigh	490	510	At crowning of head	Dorsal position; wait for signs of placenta separation	Length of third stage (min); mean blood loss (oz); PPH (≥20 oz); retained placenta (≥1 h), manual removal of placenta
2	McGinty (1956)	Delivered vaginally under Demerol or Scopolamine analgesia	Ergonovine (0·2 mg) Methergine (0·2 mg) Pitocin (5 units) (5 units) (Control 1 ml saline)	i.v. i.v i m i.v i.v	50 50 50	50	With birth of anterior shoulder	Not stated	Systolic and diastolic BP: significant elevation = 20 mmHg rise in systolic since admission; severe elevation = systolic 170 mmHg, PPH; headache, vertigo, dizziness, nausea and vomiting
3	Friedman (1957)	All vaginal deliveries except those for whom 'adequate observation was not obtained'	Pitocin (10 units) Ergonovine maleate (0·2 mg) Methergine tartrate (0 2 mg) Dihydroergotamine methane-sulfonate (1·0 mg)	i.m. i.m. or i.v. i m i m.	214 210 167 126	177	After delivery of placenta	Not stated	Uterine atony; blood loss (ml); nausea and vomiting; BP: abnormal = systolic >140 mmHg, diastolic >90 mmHg; mild elevation = rise of 15 mmHg systolic and/or 10 mmHg diastolic, moderate = rise of 25 and/or 20, severe = rise of >20

Table 1. Continued

Study					Sample size				
No	Author	Entry criteria	Drug	Route	Oxytocic	Control	Timing	Third stage management	Outcome data
4	Newton *et al.* (1961)	All term deliveries without antepartum complications and at low risk of interpartum complications	Syntocinon (1 ml)	i.m.	50	50	After delivery of placenta	Wait for placental separation, permit spontaneous expulsion by gentle fundal pressure and cord traction	Mean blood loss (ml) on delivery table and within 1 h after leaving delivery table, need for further oxytocics, mean pulse rate; subjective feelings
5	Howard *et al* (1964)	All vaginal deliveries	Oxytocin (3·0 i.u.)	i.v.	479		After delivery of placenta	Not stated	Need for further oxytocics; blood loss (ml); BP rises in diastolic and systolic <10 mmHg, 10–20 mmHg, >20 mmHg
			Methergine maleate (0·2 mg)	i v.	505				
			(Control 0·9% sodium chloride)	i.v.		475			
6	Vaughan Williams *et al* (1974)	All requiring i v infusion during labour, and expected to have spontaneous vaginal deliveries, except those with antenatal or labour complications	Ergometrine (0·5 mg)	i v.	5	10	After delivery of baby; with birth of anterior shoulder	Controlled cord traction	Central venous pressure (cm of water), blood loss (ml) in first postpartum h
			Ergometrine (0·5 mg)	i.v	10				
			Oxytocin (10 units)	i.v.	7				
			Syntometrine (1 ml)	i m.	9				
			Syntometrine (1 ml) and diazepam (10 mg)	i.m.	10				
7	Hacker & Biggs (1979)	Spontaneous vaginal deliveries; no BP >130/80 mmHg in pregnancy or labour; postpartum blood loss <200 ml	Syntometrine (oxytocin 5 i.u.+ergometrine maleate 0·5 mg)	i m.	10	6	20 min after delivery (of baby or placenta?)	Not stated	Rise in systolic and/or diastolic BP
			Ergometrine (0·5 mg)	i v.	10				

Table 1. Continued

Study					Sample size				
No	Author	Entry criteria	Drug	Route	Oxytocic	Control	Timing	Third stage management	Outcome data
8	Kerekes & Domokos (1979)	Spontaneous vaginal deliveries	$PGF_{2\alpha}$ (1 mg)	Intra-myometrial	47	43	After cord clamping	Not stated	Mean blood loss up to delivery of placenta and within subsequent 2 h (ml), Hb 48 h postpartum; mean length of third stage, uterine subinvolution; postpartum fertility
			Ergometrine 0·2 mg	i v	50				
9	Rooney *et al.* (1985)	All spontaneous deliveries 'unless excluded by a doctor'	Syntometrine (1 ml)	i.m.	346	278	With birth of anterior shoulder	50% used controlled cord traction	Blood loss (ml); transfusions; Hb; length of third stage, need for subsequent oxytocics; retained placenta, manual removal of placenta

missing data. Six authors responded to these requests for clarification.

Assessment of the methodological quality of the published studies

As well as asking authors for missing data, we also asked them to provide specific unpublished information and clarify ambiguities about their study methods. In the light of all the information available to us, each trial was reviewed to assess its methodological quality in terms of control of selection bias at entry, control of selection bias after entry, and control of observer bias in assessing outcomes.

Control of selection bias at entry. This is achieved if those responsible for enrolling participants are unable to predict which treatment will be allocated. Control of this potential bias was judged to have been successful and given high credit (***) if drugs and placebos had been prepared in a form which made them indistinguishable from each other and the randomization had been organized either by the pharmacy or by telephone. Trials in which there was a small but real chance of the next treatment being predicted or discovered by those enrolling participants (for example, those using sealed envelopes) were given intermediate credit (**). Those trials in which there was no attempt to blind treatment allocation (use of patient record numbers, birthdates, dates of admission, alternate allocation etc) were given low credit (*).

Control of selection bias after entry. Withdrawal of cases from the trial after treatment allocation, for whatever reason, may tend to introduce selection bias in the comparisons made. Control is achieved by ensuring that the primary analyses are based on data relating to *all* participants entered into the trial (***). Trials in which analyses after withdrawals were judged to have been too few to engender any material bias were given intermediate credit (**). Others were given low credit (*).

Control of assessment (observer) bias. This was also assessed. Some outcomes in perinatal trials, such as date of delivery, death and caesarean section, are unambiguous and unlikely to be subject to observer bias. Others, such as postpartum haemorrhage, may be assessed differently if the observer is aware of the trial group to which the subject has been allocated. Trials were only given full credit (***) if blinding was accomplished successfully (as in the placebo-controlled trials). Other studies in which an attempt had been made to blind observers were given intermediate credit (**). Trials in which no attempt was made to reduce assessment (observer) bias were given low credit (*).

In an attempt to control for our own subjectiveness in these judgments of methodological quality, assessments were carried out independently by two of us (W.P. and D.E.). When there were differences, these were resolved by discussion involving the third co-author (I.C.).

Table 2. Assessment of methodological quality

Study	Control of selection bias at entry	Control of selection bias after entry	Control of assessment bias
Daley (1951)	*	**	*
McGinty (1956)	**	***	*
Friedman (1957)	*	*	*
Newton *et al* (1961)	*	**	*
Howard *et al* (1964)	***	***	***
Vaughan Williams *et al* (1974)	**	*	*
Hacker & Biggs (1979)	*	***	***
Kerekes & Domokos (1979)	**	***	*
Rooney *et al* (1985)	*	**	*

Control of selection bias at entry: *** full credit; ** small but real chance of next treatment being discovered by those enrolling, * no attempt at blinding, e.g. birthdate, patient records, alternate allocation etc

Control of selection bias after entry: *** primary analysis based on all cases entered; ** analyses after withdrawals too few to engender material bias, question carefully handled; * others.

Control of assessment bias: *** blinding successful or irrelevant; ** partially blinded; * no attempt to reduce observer bias

Table 2 shows the extent to which the authors attempted to control for three types of bias. Our assessment is, of course, limited by the information which the authors have made available. Four of the papers received either full or intermediate credit for the control of selection bias at entry. The other five studies allocated the treatments in such a way that those enrolling women into the study would have known which treatment was next in line. Seven of the nine trials were given full or intermediate credit for conducting the primary analysis on *all* cases stated to have been entered, thus minimizing selection bias after entry. Assessment of outcome was blind to group allocation in only two of the nine trials. There was no evidence of any attempt to address the problem of assessment (observer) bias in the other seven trials. Table 2 also shows that there was no tendency for the methodological quality of trials in this field to improve over the 35-year period over which they have been conducted.

Statistical methods

Using methods described by Peto *et al.* (1976), Collins *et al.* (1985) and Yusuf *et al.* (1985), we analysed information derived from the trials using a procedure which has become known as 'meta-analysis' (Glass 1977). This approach is based on expressing as a ratio the odds of a negative outcome (a) versus a positive outcome (b) among women allocated to receive the intervention, with the odds of the same outcomes (a^1, b^1) among controls—the odds ratio ($a{:}b/a^1{:}b^1$). In each individual trial the odds ratio may be exaggerated or minimized because of the play of chance (especially if the intervention has only a moderate effect, or the sample size is small). In each individual trial, there is an observed value (O) and a value that might have been expected (E) if there was no difference between the effect of the interventions compared. For each trial the difference between the observed and expected values (O−E) also has a variance (Var O−E). The sum of these differences [$\Sigma\ (O_i-E_i)$] derived from several independent trials, used in combination with the sum of the variances of the differences [Σ Var (O_i-E_i)], provides a more sensitive test of the effect of the intervention and can be used to calculate a 'typical' odds ratio [$\Sigma\ (O_i-E_i)/\Sigma$ Var (O_i-E_i)].

Within each meta-analysis, trials have been ordered by their methodological quality. In this ranking, the quality of control of selection bias at entry has been given priority over the quality of control of selection bias after entry; and the latter has been given priority over control of assessment (observer) bias.

Results

We were able to obtain data on blood loss in a form suitable for an overview analysis for only five of the nine studies (Table 3, Fig. 1a). An analysis of these data suggests that routine administration of oxytocics does have an effect on the rate of postpartum haemorrhage ($P<0{\cdot}001$), reducing it by about 40%. The typical odds ratio is 0·57 with a 95% confidence interval (CI) of 0·44–0·73. (The only one of the five reports which suggests that routine oxytocics may *increase* the risk of postpartum haemorrhage is based on the trial which is weakest methodologically.) These results imply that routine oxytocic administration could reduce a postpartum haemorrhage rate of about 10% to about 6%. In other words, for every 22 women given such an oxytocic in a population which would otherwise experience a postpartum haemorrhage rate of 10%, one postpartum haemorrhage could be prevented.

Table 3. Effect of routine oxytocic administration in third stage of labour on postpartum haemorrhage (≥500 ml or 20 oz)

Study	Oxytocic	Control	Odds ratio	95% CI
Howard *et al.* (1964)	24/963	25/470	0·43	0·23–0·78
McGinty (1956)	1/150	5/50	0·04	0·01–0·27
Daley (1951)	45/490	80/510	0·55	0·38–0·80
Rooney *et al.* (1985)	34/346	42/278	0·61	0·38–0·99
Friedman (1957)	24/717	2/177	2·19	0·82–5·83
Typical odds ratio			0·57	0·44–0·73

CI, Confidence interval.

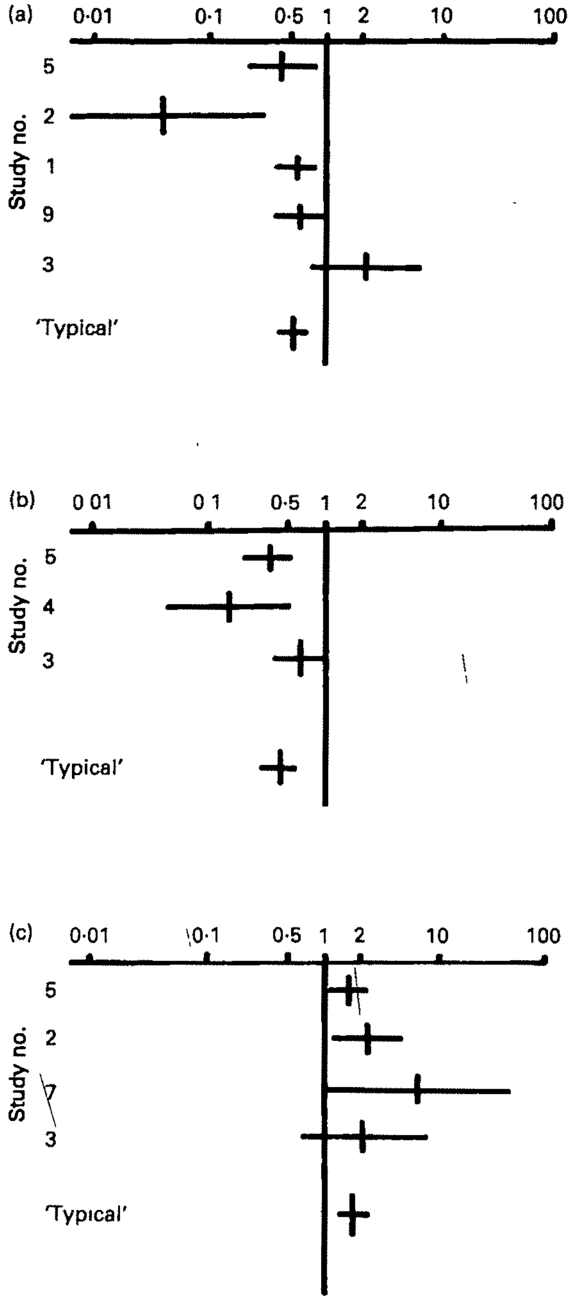

Fig. 1. Effect of routine oxytocic administration in third stage of labour on (a) postpartum haemorrhage (Table 3), (b) the need for further oxytocic administration (Table 4), (c) blood pressure elevation (Table 5). ——+— indicates the odds ratio with the 95% confidence interval The study number codes are listed in Table 1.

Table 4. Effect of routine oxytocic administration in third stage of labour on the need for further oxytocic administration

Study	Oxytocic	Control	Odds ratio	95% CI
Howard *et al* (1964)	46/984	58/475	0·32	0·21–0·49
Newton *et al.* (1961)	1/50	11/50	0·15	0·05–0·51
Friedman (1957)	100/717	36/177	0·61	0·39–0·96
Typical odds ratio			0·40	0·30–0·55

CI, Confidence interval

In the light of this finding it is not surprising that routine prophylaxis with oxytocics appeared to result in a reduced need to use these drugs therapeutically (Table 4, Fig. 1b). The comparisons from the three trials for which data could be obtained generated a typical odds ratio of 0·40 with a 95% CI of 0·30–0·55.

The effect of the policy on the risks of retained placenta remains far from clear. We were able to obtain information about retained placenta and manual removal of the placenta from only two studies (Daley 1951; Rooney *et al.* 1985) and these cannot be assumed to be representative. Although there is some suggestion from these limited data that routine administration of oxytocics reduces the risk of retained placenta, this could easily reflect selective presentation of outcome data or the play of chance. One other trial (Kerekes & Domokos 1979) provides evidence of possible relevance in that the mean duration of the third stage was longer in the control group (7·3 min) than in a group given ergometrine (5·7 min) and a group given $PGF_{2\alpha}$ (3·9 min). The 99% CI of these estimates do not overlap.

Only two of the studies analysed (McGinty 1956; Friedman 1957) provided information about hypertension (defined as over 170 mmHg systolic, or over 140 mmHg and 90 mmHg diastolic, respectively). In each of these studies a statistically significant hypertensive effect of oxytocics was demonstrated. In four studies, data were available on blood pressure more generally (Table 5, Fig. 1c). Analysis of these data suggests that the prophylactic use of oxytocics leads to a rise in blood pressure (typical odds ratio 1·76, 95% CI 1·33–2·33). These results support the suggestion that oxytocics increase the risk of hypertension; but they may also partly reflect the fact that these drugs reduce the risk of hypotension caused by blood loss. Finally, it is relevant to note that Vaughan Williams *et al.* (1974) showed that there was a significant rise in central venous pressure after the administration of ergometrine or Syntometrine but no significant effect of either oxytocin or of Syntometrine when preceded by diazepam.

Discussion

In the triennium 1979–1981, nine out of the 217 direct maternal deaths (4·1%) were attributed to postpartum haemorrhage—a rate of $5/10^6$ maternities (Report on Confidential Enquiries 1986). The estimated 2% incidence of postpartum

Table 5. Effect of routine oxytocic administration in third stage of labour on blood pressure elevation

Study	Oxytocic	Control	Odds ratio	95% CI
Howard *et al* (1964) (systolic or diastolic >20 mmHg)	158/983	50/475	1·57	1·15–2·15
McGinty (1956) (systolic ⩾20 mmHg)	43/150	6/50	2·45	1·17–5·15
Hacker & Biggs (1979) (systolic or diastolic >20 mmHg)	9/20	0/6	6·77	1·03–44·38
Friedman (1957) (systolic >25 or diastolic >20 mmHg)	14/717	1/177	2·32	0·64–8·33
Typical odds ratio			1·76	1·33–2·33

CI, Confidence interval

haemorrhage for 1980 as given in the latest report of the Maternity Hospital In-Patient Enquiry (1986) almost certainly underestimates the true extent of the problem, however (Hall *et al.* 1985; Gilbert *et al.* 1987).

Our analysis supports the hypothesis that routine use of oxytocic drugs in association with management of the third stage of labour reduces the risk of postpartum haemorrhage and the need for the administration of oxytocics later, but increases the risk of provoking hypertension. In the light of the variable methodological quality of the trials reviewed, it is reassuring that these conclusions are in accord with those based on the particular trial (Howard *et al.* 1964) which we judged to be least subject to certain biases.

The evidence presented is likely to provide the least biased estimates currently available of the effects of using oxytocics routinely in managing the third stage of labour. It is obviously possible that bias has been introduced by our inability to include in all our overview analyses data from each and every one of the trials reported. Bias may also have resulted from selective publication of those trials which showed significant differences between the two policies (Begg 1985; Chalmers 1985). Unfortunately, there is no way in which we can assess either of these possibilities without access to the unpublished data.

We are confident, however, that our analysis has provided a more valid estimate of the likely reduction in postpartum haemorrhage rates achievable with a policy of routine oxytocic administration than estimates derived from studies which have used historical controls. Such studies have suggested that the introduction of routine oxytocic prophylaxis results in a reduction in the rate of postpartum haemorrhage of up to 90% (Lister 1950; Martin & Dumoulin 1953). The evidence reviewed here suggests that this is likely to be a considerable overestimate: the reduction seems more likely to be of the order of 40%. We believe that this level of reduction in the incidence of a serious and not uncommon complication of childbirth is nevertheless of great importance.

This advantage of the policy must be considered together with the rare but serious morbidity which has sometimes been attributed to oxytocic administration. Maternal deaths from cardiac arrest (Report on Confidential Enquiries 1975) and intracerebral haemorrhage (Ringrose 1962) have been attributed to ergometrine, as have non-fatal instances of cardiac arrest and myocardial infarction (Browning 1974; Valentine 1977; Taylor & Cohen 1985), postpartum eclampsia (Hofmeister & Brown 1953; McFadyen 1960; Abouleish 1976), and pulmonary oedema in cardiac patients (Casady *et al.* 1960; Dumoulin 1981) as a result of the venous vasoconstriction which is known to occur with ergometrine (Brooke & Robinson 1970; Greenhalf & Evans 1970; Vaughan Williams *et al.* 1974).

Because these events are so rare the available randomized trials cannot provide useful estimates of the extent to which they may be attributable to oxytocic administration, but the widespread practice of withholding oxytocics (particularly ergometrine) from women known to be at increased cardiovascular risk seems prudent.

Certain other rare but definite adverse consequences of routine oxytocic administration include intrauterine asphyxia of an undiagnosed second twin (Dunn 1966c), and neonatal convulsions in a baby mistakenly injected with an oxytocic instead of prophylactic vitamin K (Whitfield & Salfield 1980; Pandey & Haines 1982).

In principle, randomized trials should be able to provide useful information about adverse effects which are less serious but more prevalent. In fact, the nine studies reviewed here provided little usable information in this respect. Five of the trials made some mention of possible adverse effects, but apart from the investigation of hypertensive effects, there were few systematic attempts to quantify side-effects. Howard *et al.* (1964) merely reported a 'paucity of subjective side-effects'. Daley (1951) stated that there were none. Newton *et al.* (1961) asked their patients 'How do you feel?', half an hour after treatment, and the proportion who answered positively or negatively did not differ between the two trial arms. Only one woman in the McGinty (1956) trial complained of nausea, vomiting and headache. Friedman (1957) reported no significant differences in nausea and vomiting between controls and the oxytocin and dihydroergotamine groups, but did note statistically significantly more unpleasant symptoms in the ergonovine and methergine groups. In view of the fact that ergometrine is known to lower serum prolactin levels (Shane & Naftolin 1974; Weiss *et al.* 1975; Canales *et al.* 1976), it is particularly unfortunate that none of the trials has investigated whether or not ergot alkaloids interfere with breast-feeding.

On balance, the known benefits of routine oxytocic administration outweigh the likely risks in women who are not at increased cardiovascular risk. However, most of the data on which this conclusion is based have been gathered in circumstances in which the type of management of the third stage of labour was not documented. As we noted at the beginning of this paper, there are reasons for supposing that other elements of active management (dorsal position, early cord clamping, and controlled cord traction) may predispose to the problems which routine oxytocic administration would otherwise prevent. We are currently analysing the results of a randomized trial to test this and other hypotheses related to the postulated advantages of encouraging a physiological approach to placental delivery.

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References

Abouleish, E. (1976) Postpartum hypertension and convulsion after oxytocic drugs. *Anesth Analg* **55**, 813-815.

Baillie, W T. (1963) Vasopressor activity of ergometrine maleate in anaesthetised parturient women. *Br Med J* **i**, 585-588.

Barbaro, C. A. & Smith, G. O. (1961) Clinical trial of SE505—a new oxytocic mixture. *Aust NZ J Obstet Gynaecol* **1**, 147-150

Beischer, N. A. & Mackay, E. V. (1986) *Obstetrics and the Newborn,* Baillière Tindall, Eastbourne, pp. 262-269.

Begg, C B. (1985) A measure to aid in the interpretation of published clinical trials. *Stat Med* **4**, 1-9.

Bender, S. & Tindall, V. R. (1980) *Practical Student Obstetrics,* Heinemann, London, p. 209

Bonham, D. G (1963) Intramuscular oxytocics and cord traction in the third stage of labour *Br Med J* **ii**, 1620-1623.

Brooke, O G. & Robinson, B F. (1970) Effect of ergotomine and ergometrine in forearm venous compliance in man. *Br Med J* **i**, 139-142.

Browning, D. J. (1974) Serious side effects of ergometrine and its use in routine obstetric practice. *Med J Aust* **1**, 957-959

Canales, E. S., Garrido, J. T , Zarate, A , Mason, M. & Soria, J. (1976) Effect of ergonovine on prolactin secretion and milk let down. *Obstet Gynecol* **48**, 228-229.

Casady, G. N., Moore, D. C & Brindenbaugh, L. D. (1960) Postpartum hypertension after use of vasoconstrictor and oxytocic drugs. *JAMA* **172**, 101-105.

Chalmers, I (1985) Proposal to outlaw the term 'negative trial' *Br Med J* **290**, 1002

Chalmers, I., Hetherington, J., Newdick, M , Mutch, L , Grant, A., Enkin, M., Enkin, E. & Dickersin, K. (1986) A register of controlled trials in perinatal medicine. *Controlled Clin Trials* **7**, 306-324

Chamberlain, G. V. P (1985) Discussion In *Litigation and Obstetrics and Gynaecology* (Chamberlain, G. V. P., Orr, C. J. B & Sharp, F., eds), Royal College of Obstetricians and Gynaecologists, London, p. 272.

Chukudebelu, W. O., Marshall, A. T. & Chalmers, J. A. (1963) Use of 'syntometrine' in the third stage of labour *Br Med J* **i**, 1390-1391.

Clayton, S. G., Lewis, T. L. T & Pinker, G. (1980) *Obstetrics by Ten Teachers,* Edward Arnold, London, pp. 124-126.

Collins, R., Yusuf, S. & Peto, R. (1985) Overview of randomised trials of diuretics in pregnancy. *Br Med J* **290**, 17-23

Conn, L C., Vant, J. R & Cantor, M. M. (1941) A critical analysis of blood loss in 2,000 obstetric cases *Am J Obstet Gynecol* **42**, 768.

Daley, D. (1951) The use of intramuscular ergometrine at the end of the second stage of normal labour. *J Obstet Gynaecol Br Emp* **58**, 388-397

Dickersin, K., Hewitt, P , Mutch, L., Chalmers, I. & Chalmers, T. C. (1985) Perusing the literature: comparison of MEDLINE searching with a Perinatal Trials Database. *Controlled Clin Trials* **6,** 306-317

Docherty, P W. & Hooper, M (1981) Choice of an oxytocic agent for routine use at delivery *J Obstet Gynaecol* **2,** 60

Dudley, H. W & Moir, J. C (1935) The substance responsible for the traditional clinical effect of ergot *Br Med J* **i,** 520-523.

Dumoulin, J. G (1981) A reappraisal of the use of ergometrine *J Obstet Gynaecol* **1,** 178-181.

Dunn, P. M (1966*a*) The placental venous pressure during and after the third stage of labour following early cord ligation. *J Obstet Gynaecol Br Commonw* **73,** 747-756.

Dunn, P M. (1966*b*) Postnatal placental respiration. *Dev Med Child Neurol* **8,** 607

Dunn, P. M (1966*c*) Ergometrine and the undiagnosed twin. *Br Med J* **ii,** 1535.

Dunn, P. M. (1973) Caesarean section and the prevention of respiratory distress syndrome of the newborn. In *Perinatal Medicine* (Bossart H., Cruz, J. M , Huber, A., Prud'hom, L. S. & Sistek, J. eds), Hans Huber, Vienna, pp. 138-145.

Dunn, P. M. (1985) Management of childbirth in normal women: the third stage and fetal adaptation In *Perinatal Medicine*, (Clinch, J. & Matthews, T , eds), Report of the IX European Congress on Perinatal Medicine, Dublin, MTP Press, Lancaster, pp. 47-54.

Dunn, P. M., Fraser, I. D & Raper, A. B. (1966) Influence of early cord ligation on the transplacental passage of foetal cells. *J Obstet Gynaecol Br Commonw* **73,** 757-760.

Du Vigneaud, V., Ressler, C. & Tippet, S. (1953) The sequence of amino acids in oxytocin with a proposal for the structure of oxytocin *J Biol Chem* **205,** 949.

Elbourne, D , Prendiville, W & Chalmers, I (1988) Choice of oxytocic preparation for routine use in the management of the third stage of labour: an overview of the evidence from controlled trials. *Br J Obstet Gynaecol* **95,** 17-30

Embrey, M. P., Barber, D T C. & Scudamore, J. H (1963) Use of syntometrine in prevention of post partum haemorrhage *Br Med J* **i,** 1387-1389

Fleigner, J. R & Hibbard, B. M. (1966) Active management of the third stage of labour. *Br Med J* **ii,** 622-623

Forster, F M. C. (1957) A comparative study of ergometrine and 'Methergin' used in the management of the third stage of labour. *Med J Aust* **2,** 155-156.

Francis, H H., Miller, J M. & Porteous, C R (1965) Clinical trial of an oxytocin-ergometrine mixture. *Aust NZ J Obstet Gynaecol* **5,** 47-51

Friedman, E. A (1957) Comparative clinical evaluation of postpartum oxytocics *Am J Obstet Gynecol* **73,** 1306-1313

Fugo, N. W. & Dieckmann, W. J (1958) A comparison of oxytocic drugs in the management of the placental stage. *Am J Obstet Gynecol* **76,** 141-146.

Garcia, J., Garforth, S & Ayers, S. (1987) The policy and practice of midwifery study· introduction and methods. *Midwifery* **3,** 2-9.

Gilbert, L., Porter, W. & Brown, V (1987) Postpartum haemorrhage—a continuing problem *Br J Obstet Gynaecol* **94,** 67-71.

Gilliat, W. (1949) *Transactions of the 12th Congress of Obstetrics and Gynaecology,* p. 271

Glass, G. V (1977) Integration findings the meta-analysis of research. *Rev Res Education* **5,** 351-379

Greenhalf, J. O. & Evans, D. J. E (1970) Effect of ergometrine on the central venous pressure in the third stage of labour *J Obstet Gynaecol Br Commonw* **77,** 1066-1069

Greenhill, J P. (1951) *Year Book of Obstetrics and Gynaecology,* Year Book, Chicago, p. 230

Groeber, W. R. & Bishop, E. H. (1960) Methergine and ergonovine in the third stage of labor *Obstet Gynecol* **15,** 85-88

Hacker, N. F & Biggs, J S. G. (1979) Blood pressure changes when uterine stimulants are used after normal delivery *Br J Obstet Gynaecol* **86,** 633-636

Hall, M H., Halliwell, R & Carr-Hill, R (1985) Concomitant and repeated happenings of complications of the third stage of labour. *Br J Obstet Gynaecol* **92,** 732-738

Hamilton, H. G., Higgins, R S & Alsop, W. S. (1952) A comparative clinical study of naturally derived and synthetic oxytocic drugs of ergot origin *South Med J* **45,** 728-731.

Hendricks, C H. & Brenner, W. E. (1970) Cardiovascular effects of oxytocic drugs used postpartum *Am J Obstet Gynecol* **108,** 751-768.

Hibbard, B. M. (1964) The third stage of labour *Br Med J* **ii,** 1485-1488.

Hickman, M. A. (1978) *An Introduction to Midwifery.* Blackwell Scientific Publications, Oxford, pp. 166-168.

Hofmeister, F. J. & Brown, R. C. (1953) Postpartum convulsions. *Am J Obstet Gynecol* **65,** 498-504.

Howard, W. F , McFadden, P. R & Keettel, W. C. (1964) Oxytocic drugs in fourth stage of labor. *JAMA* **189,** 411-413.

Inch, S. (1985) Management of the third stage of labour—another cascade of intervention? *Midwifery* **1,** 114-122.

Johnstone, M. (1972) The cardiovascular effects of oxytocic drugs *Br J Anaesth* **44,** 826-833.

Kerekes, L & Domokos, N (1979) The effect of prostaglandin F2-alpha on third stage labour. *Prostaglandins* **18,** 161-166.

Kerr, J. M. M. & Moir, J. C. (1949) *Operative Obstetrics,* Baillière, Tindall & Cox, London, pp. 54 and 810.

Kimbell, N (1958) Brandt-Andrews technique of delivery of the placenta. *Br Med J* **i,** 203-204.

Lister, U. M. (1950) The use of intravenous oxytocics in the second stage of labour *J Obstet Gynaecol Br Emp* **57**, 210-222.

Llewellyn Jones, D. (1986) *Fundamentals of Obstetrics and Gynaecology*, 4th edn, Vol 1, Faber & Faber, London, pp. 135-136

Marsh, G. N. (ed) (1985) *Modern Obstetrics in General Practice*, Oxford University Press, Oxford

Martin, J. D & Dumoulin, J. G. (1953) Use of intravenous ergometrine to prevent post partum haemorrhage *Br Med J* **i**, 643-646.

Maternity Hospital In-Patient Enquiry (1986) *Maternity Tables 1977–1981 England and Wales*, HMSO, London.

McFadyen, I. R (1960) Postpartum pre-eclampsia. *Lancet* **ii**, 1009-1010.

McGinty, L. B (1956) A study of the vasopressor effects of oxytocics when used intravenously in the third stage of labour. *West J Surg* **64**, 22-28.

Milton, P J. D (1985) Natural childbirth and home deliveries—clinical aspects In *Litigation and Obstetrics and Gynaecology* (Chamberlain, G. V P., Orr, C J. B & Sharp, F., eds), Royal College of Obstetricians and Gynaecologists, London, pp. 279-299.

Moir, J C (1932) The action of ergot preparation on the puerperal uterus. *Br Med J* **i**, 1119-1122.

Moir, J. C. (1955) The history of present day use of ergot. *Can Med Assoc J* **72**, 727-734.

Moir, J. C (1964) The obstetrician bids and the uterus contracts. *Br Med J* **ii**, 1025-1029.

Moir, D D & Amoa, A. B. (1979) Ergometrin or oxytocin? *Br J Anaesth* **51**, 113-116.

Moore, J H. (1956) Is methylergonovine tartrate superior to ergonovine maleate? *Am J Obstet Gynecol* **71**, 908-911.

Myles, M. F (1985) *Textbook for Midwives*, 10th edn, Churchill Livingstone, Edinburgh, pp. 331-336

National Perinatal Epidemiology Unit (1985) *A Classified Bibliography of Controlled Trials in Perinatal Medicine 1940-1984* Oxford University Press, Oxford.

Nelson, G H. (1983) Use of 15-methyl prostaglandin F2-alpha postpartum to contract the uterus in normal pregnant women. *J Med Assoc Ga* **72**, 703-706.

Newton, M., Mosey, L. M , Egli, G. E , Gifford, W. B. & Hull, C T. (1961) Blood loss during and immediately after delivery. *Obstet Gynecol* **17**, 9-18.

Nieminen, U. & Jarvinen, P. A. (1963) A comparative study of different medical treatments of the third stage of labour. *Ann Chir Gynaecol Fenn* **53**, 424-429

Pandey, S. K. & Haines, C. I. (1982) Accidental administration of ergometrine to a newborn infant. *Br Med J* **285**, 693.

Paull, J D. & Ratten, G. J (1977) Ergometrine and third stage blood loss. *Med J Aust* **1**, 178-179.

Peto, R., Pike, M. C , Armitage, P. *et al.* (1976) Design and analysis of randomised clinical trials requiring prolonged observation of each patient I. Introduction and design. *Br J Cancer* **34**, 585-612.

Report on Confidential Enquiries into Maternal Deaths 1970–1972 (1975) HMSO, London, p. 68

Report on Confidential Enquiries into Maternal Deaths 1979-1981 (1986) HMSO, London, pp 22-29

Ringrose, C. A. D. (1962) The obstetrical use of ergot *Can Med Assoc J* **87**, 712-714.

Rooney, I., Hughes, P. & Calder, A (1985) Is routine administration of syntometrine still justified in the management of the third stage of labour? *Health Bull* **43/3**, 99-101.

Shane, J. M. & Naftolin, F (1974) Effect of ergonovine maleate on puerperal prolactin *Am J Obstet Gynecol* **120**, 129-131

Soiva, K & Koistinen, U. (1964) Clinical experience with simultaneous intramuscular injection of oxytocin and methylergometrine. *Ann Chir Gynaecol* **53**, 173-186.

Sorbe, B. (1978) Active pharmacologic management of the third stage of labor. *Obstet Gynecol* **52**, 694-697

Spencer, P. M. (1962) Controlled cord traction in management of the third stage of labour. *Br Med J* **i**, 1728-1732.

Stearn, R H. (1963) Syntometrine in the management of the third stage of labour. *J Obstet Gynaecol Br Commonw* **70**, 593-596

Symes, J. B. (1984) A study on the effect of ergometrine on serum prolactin levels following delivery *J Obstet Gynaecol* **5**, 36-38.

Taylor, G. J & Cohen, B. (1985) Ergonovine-induced coronary artery spasm and myocardial infarction after normal delivery. *Obstet Gynecol* **66**, 821-822

Turnbull, A C. (1976) Obstetrics—traditional use of ergot compounds. *Postgrad Med J* **52 (Suppl. 1)**, 15-16

Valentine, B. H , Martin, M A. & Phillips, N V. (1977) Collapse during operation following intravenous ergometrine *Br J Anaesth* **49**, 81-82.

Vaughan Williams, C., Johnson, A. & Ledward, R. (1974) A comparison of central venous pressure changes in the third stage of labour following oxytocic drugs and diazepam *J Obstet Gynaecol Br Commonw* **81**, 596-599

Weiss, G., Klein, S , Shenkman, L., Katooka, K & Hollander, C S. (1975) Effect of methylergonovine on puerperal prolactin secretion. *Obstet Gynecol* **46**, 209-210.

Whitfield, M F & Salfield, S A. W. (1980) Accidental administration of syntometrine in adult dosage to the newborn. *Arch Dis Child* **55**, 68-70

Yusuf, S., Peto, R., Lewis, T., Collins, R. & Sleight, P (1985) Beta blockade during and after myocardial infarction: an overview of the randomised trials. *Prog Cardiovasc Dis* **XXVII, 5**, 336-371.

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Choice of oxytocic preparation for routine use in the management of the third stage of labour: an overview of the evidence from controlled trials

DIANA ELBOURNE, WALTER PRENDIVILLE, IAIN CHALMERS

Summary. Prophylactic use of oxytocics reduces the risk of postpartum haemorrhage by about 40%. The analysis presented in this paper assesses which oxytocic preparation is associated with the least risk of postpartum haemorrhage and examines the relative effects of different preparations on the length of the third stage, the risk of manual removal of the placenta, blood pressure and other side-effects. A mixture of oxytocin and ergometrine (Syntometrine) appears to be the safest and most effective prophylactic of the alternatives which have been compared, but the quality of the evidence is not satisfactory. There is scope for a randomized comparison of Syntometrine with oxytocin to obtain unbiased and more precise estimates of their relative effects on postpartum haemorrhage, blood pressure and unpleasant side-effects.

This is the second of two papers in which we present analyses based on data derived from controlled trials mounted to assess the effects of routine administration of oxytocic drugs in the management of the third stage of labour In our previous paper (Prendiville *et al.* 1988) we presented evidence suggesting that oxytocic drugs used routinely in this way reduce the risk of postpartum haemorrhage by about 40%, and noted that the available data were insufficient to assess the effects of this policy on the incidence of retained placenta, hypertension and other possible adverse effects.

Although routine use of oxytocics has become widespread, the choice of oxytocic preparation varies. Thus oxytocin is used in much of North America (M. Enkin, personal communication), ergometrine is used widely in Denmark (F. Børlum Kristensen, personal communications), and Syntometrine (a mixture of oxytocin and ergometrine) is the most popular oxytocic preparation used in Britain (Garcia *et al.* 1987)

In this paper we report an analysis of data derived from controlled trials in which the effects of different oxytocic preparations on postpartum haemorrhage and on unwanted effects such as hypertension have been compared.

Materials and methods

Identification and selection of relevant studies

Twenty-seven trials involving four categories of oxytocics (ergot alkaloids, oxytocin, prostaglandins and Syntometrine) in the management of the third stage were identified in 26 papers published between 1956 and 1984 using the Oxford Database of Perinatal Trials (National Perinatal Epidemiology Unit 1985; Dickersin *et al* 1985, Chalmers *et al.* 1986) Ten were excluded from further analyses because either they did not use a quasi-random design (Chukudebelu *et al.* 1963; Stearn 1963, both

National Perinatal Epidemiology Unit, Radcliffe Infirmary, Oxford OX2 6HE
DIANA ELBOURNE *Social Statistician*
IAIN CHALMERS *Director*

Department of Obstetrics and Gynaecology, Bristol Maternity Hospital, Southwell Street, Bristol BS2 8EG
WALTER PRENDIVILLE *Lecturer*

Correspondence Walter Prendiville

Table 1. Clinical characteristics of the studies

Study No	Study Author	Entry criteria	Drug	Route	Timing	Sample size	Third stage management	Outcome data
1	McGinty (1956)	Delivered vaginally under Demerol or Scopolamine analgesia	Ergonovine (0·2 mg)	i.v.	With birth of anterior shoulder	50	Not stated	Systolic and diastolic BP· significant elevation = 20 mmHg rise in systolic since admission, severe elevation = systolic > 170 mmHg, PPH; headache, vertigo; dizziness; nausea and vomiting
			Methergine (0·2 mg)	i.v.	With birth of anterior shoulder	50		
			Pitocin (5 units) (5 units)	 i.m. i.v.	With birth of anterior shoulder	50		
2	Friedman (1957)	All vaginal deliveries except those for whom 'adequate observation was not obtained'	Oxytocin (10 units)	i.m.	After delivery of placenta	214	Not stated	Uterine atony; blood loss (cc); nausea and vomiting; BP· abnormal = systolic > 140 mmHg, diastolic >90 mmHg, mild elevation = rise of 15 mmHg systolic and/or 100 mmHg diastolic, moderate = rise of 25 and/or 20, severe = rise of >20
			Ergonovine maleate (0·2 mg)	i.m. or i.v.	After delivery of placenta	210		
			Methergine tartrate (0·2 mg)	i.m. or i.v.	After delivery of placenta	167		
			Dihydro-ergotamine methane-sulfonate (1·0 mg)	i.m.	After delivery of placenta	126		

Table 1. *continued (1)*

3	Fugo & Dieckmann (1958)	Not stated	U3772 (80 mg)	i.v.	When anterior shoulder visible	151	MRP if placenta undelivered in 10 min, 'shoehorn' if placenta protruding and traction	Time/delivery of placenta after oxytocic; blood loss (cc/ml), BP; subjective side-effects
			Syntocinon (2 i.u.)	i.v.	When anterior shoulder visible	156		
			Ergonovine (4 mg)	i.v	When anterior shoulder visible	149		
			Pitocin (2 i.u.)	i v	When anterior shoulder visible	168		
4	Barbaro & Smith (1961)	All vaginal deliveries >28 weeks	SE505 (5 units syntocin and 0·5 mg ergometrine maleate in 1 ml)	i.m.	Immediately after delivery of fetus	300	Not stated	Mean loss (clinical estimation); PPH (>600 ml); mean length of third stage (min)
			Ergometrate-maleate (0·5 mg) + ergometrine maleate (0·5 mg)	i.v.	Immediately after delivery of fetus. After delivery of placenta	300		
5	Bonham (1963)	All vaginal deliveries except multiple pregnancies, previous PPH or MRP forceps, breech, parity ≥4, syntocinon infusions in first or second stages	Ergometrine (0·5 mg)	i.m.	At crowning of head	217	Half controlled cord traction, half maternal effort, fundal pressure (classical pistoning technique)	Blood loss (including loss on linen and swabs), loss recorded in 20 ml steps above 100 ml; PPH (≥568 ml); mean loss; length of third stage; manual removal of placenta
			Ergometrine (0.5 mg) + hyaluronidase (1500 units)	i.m.	At crowning of head	177		
			Ergometrine (0·5 mg) + oxytocin (5 units)	i.m.	At crowning of head	199		

Table 1. *continued (2)*

Study								
No.	Author	Entry criteria	Drug	Route	Timing	Sample size	Third stage management	Outcome data
6	Nieminen & Jarvinen (1963)	Not stated	OCM 505 (methergin 0·5 mg + syntocinon 5 i.u)	i.m	With delivery of anterior shoulder	689	Active	Duration of third stage (min); haemorrhage; retained placenta
			Methergin (0·1–0·2 mg)	i v	With delivery of anterior shoulder	689		
			Syntocinon (5 i.u)	i m	With delivery of anterior shoulder	689		
7	Howard *et al* (1964)	All vaginal deliveries	Oxytocin (3·0 i u)	i v	After delivery of placenta	479	Not stated	Need for further oxytocics; blood loss (ml), BP rises in diastolic & systolic <10 mmHg, 10–20 mmHg, >20 mmHg
			Methergine maleate (0·2 mg)	i v	After delivery of placenta	505		
8	Soiva & Koistinen (1964)	Spontaneous singleton cephalic deliveries	Syntometrine	i m.	Immediately after birth of baby	560	No efforts to express placenta during first third stage contraction	Blood loss (g), PPH (>500 g); length of third stage, retained placenta; MRP; puerperal complications
			Methergin (0·12–0·2 mg)	i v	Immediately after birth of baby	280 (+280 historical controls)		

Table 1. *continued (3)*

9	Francis *et al* (1965*a*)	All except previous blood loss >20 oz, instrumental deliveries, breeches, twins, APH, severe anaemia, i.v. oxytocin in first and second stages	Ergometrine (0·5 mg)	i.m.	After delivery of placenta	300	Brandt-Andrews after signs of descent	Blood loss (oz) including swabs, retained placenta (not delivered within 20 min)
			Syntometrine (0·5 ml)	i.m.	After baby born and cord divided	287		
			Syntometrine (1·0 ml)	i.m	After baby born and cord divided	300		
10	Francis *et al* (1965*b*)	As above	Ergometrine (0·5 mg) + water (1·0 ml)	i.m. i.m.	End of second stage End of third stage	183	As above	As above
			Syntometrine (1·0 ml) + water (1·0 ml)	i.m. i.m.	End of second stage End of thrid stage	171		
			Water (1·0 ml) + ergometrine (0·5 ml)	i.m. i.m	End of second stage End of third stage	167		
11	Vaughan Williams *et al.* (1974)	All requiring i.v infusion during labour, and expected to have spontaneous vaginal deliveries, except those with antenatal or labour complications	Ergometrine (0·5 mg)	i.v	After delivery of baby	5	Controlled cord traction	Central venous pressure (cm of water), blood loss (ml) in first h postpartum
			Ergometrine (0 5 mg)	i.v.	With delivery of anterior shoulder	10		
			Oxytocin (10 units)	i.v	With delivery of anterior shoulder	7		
			Syntometrine (1 ml)	i.m.	With delivery of anterior shoulder	9		
			Syntometrine (1 ml) + diazepam (10 mg)	i.m	With delivery of anterior shoulder	10		

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Table 1. *continued (4)*

Study								
No	Author	Entry criteria	Drug	Route	Timing	Sample size	Third stage management	Outcome data
12	Sorbe (1978)	Not stated	Oxytocin (10 i u.)	i v.	After delivery of anterior shoulder	506	Not stated	Blood loss (ml); PPH (>600 ml), Crede's manoeuvre MRP; length of third stage; placental retention
			Ergometrine (0·2 mg)	i v.	After delivery of anterior shoulder	543		
13	Kerekes & Domokos (1979)	Spontaneous vaginal deliveries	PGF$_{2\alpha}$ (1 mg)	Intra-myometrial	After cord clamping	47	Not stated	Mean blood loss up to delivery of placenta and within subsequent 2 h (ml); Hb 48 h postpartum, mean length of third stage, uterine subinvolution; postpartum fever
			Ergometrine (0 2 mg)	i v.	After cord clamping	50		
14	Hacker & Biggs (1979)	Spontaneous vaginal deliveries, no BP>130/80 mmHg in pregnancy or labour, postpartum blood loss <200 ml	Syntometrine (oxytocin 5 i.u + ergometrine maleate 5 mg)	i.m	20 min after delivery	10	Not stated	Rise in systolic and/or diastolic BP
			Ergometrine (0·5 mg)	i v.	20 min after delivery	10		

Table 1. *continued (5)*

15	Dumoulin (1981)	Caesarean sections excluded, otherwise not stated	Syntometrine	i.m.	After delivery of head	1000	Not stated	Primary PPH; mean blood loss (ml); secondary PPH, manual removal of placenta
			Oxytocin (5 i.u.)	i.m.	After delivery of head	250		
			Oxytocin (10 i u.)	i m	After delivery of head	500		
16	Docherty & Hooper (1981)	Normal patients, spontaneous vertex deliveries without episiotomies; oxytocin infusions, if used in labour, were stopped at delivery	Oxytocin (10 units)	i.m.	Not stated	25	Not stated	Mean blood loss (ml); nausea; vomiting
			Ergometrine maleate (0·5 mg) + oxytocin (5 units)	i m		25		
17	Symes (1984)	Primigravidae vaginal deliveries	Oxytocin (5 units) + ergometrine (0·5 mg)	i m	With delivery of anterior shoulder	5	Not stated	Serum prolactin
			Oxytocin (5 units)	i m.	With delivery of anterior shoulder	6	Active	

involving comparisons of different consultants), or because the relevant comparisons were between oxytocics of the same type (Moore 1956; Forster 1957; Groeber & Bishop 1960; Paull & Ratten 1977 (only ergot alkaloids); Nelson 1983 (only prostaglandins)) or with a non-oxytocic control (Daley 1951; Newton *et al.* 1961; Rooney *et al.* 1985). The following 17 trials reported in 16 papers remained for further analysis: McGinty (1956); Friedmann (1957); Fugo & Dieckmann (1958); Barbaro & Smith (1961); Bonham (1963); Nieminen & Jarvinen (1963); Howard *et al.* (1964); Soiva & Koistinen (1964); Francis *et al.* (1965) (one paper reporting two trials); Vaughan Williams *et al.* (1974); Sorbe (1978), Hacker & Biggs (1979); Kerekes & Domokos (1979); Docherty & Hooper (1981); Dumoulin (1981); and Symes (1984).

The clinical characteristics of the studies are described in Table 1. The reports were published over a period of 27 years (1957–1984). The sample sizes of individual trials ranged from 11 to 2067 women. The criteria for entry also varied considerably, as did the more general management of the third stage and the outcomes which were considered. The route of administration was usually intramuscular or intravenous (only one being into the myometrium), and the timing varied from crowning of the head, delivery of the anterior shoulder, to completion of the second and third stages of labour.

Ergot alkaloids and oxytocin were compared in seven trials (McGinty 1956; Friedman 1957; Fugo & Dieckmann 1958; Nieminen & Jarvinen 1963; Howard *et al.* 1964; Vaughan Williams *et al.* 1974; and Sorbe 1978). Syntometrine was compared with ergot alkaloids in nine trials (Barbaro & Smith 1961; Bonham 1963, Nieminen & Jarvinen 1963; Soiva & Koistinen 1964; Francis *et al.* 1965 *a* & *b*; Vaughan Williams *et al.* 1974; Hacker & Biggs 1979; and Docherty & Hooper 1981). Syntometrine was compared with oxytocin in five trials (Nieminen & Jarvinen 1963; Vaughan Williams *et al.* 1974; Docherty & Hooper 1981, Dumoulin 1981; Symes 1984). Only one study (Kerekes & Domokos 1979) compared an ergot alkaloid with a prostaglandin. There were no comparisons of prostaglandins with either oxytocins or Syntometrine.

Attempts to obtain missing data

The authors of those six trials in which there was also a non-oxytocic control (McGinty 1956; Friedmann 1957; Howard *et al* 1964; Vaughan Williams *et al.* 1974; Hacker & Biggs 1979 and Kerekes & Domokos 1979) were contacted for further information. Replies were obtained from three of them.

Assessment of the methodological quality of the published studies

In our earlier paper (Prendiville *et al.* 1988) we described our method of assessing the methodological quality of the trials included in our analysis, and rationale for this assessment and the inevitable element of subjectivity which the assessment involves.

Table 2 shows the extent to which the authors attempted to control for three types of bias in the studies used in the present overview. We gave eight of the trials either full or intermediate credit for the control of selection bias at entry. To the extent that it was possible to assess this, it appeared that in 13 of the 17 trials the primary analysis was based on all cases entered. Finally, assessment of the primary outcome was blind to group allocation in six trials, and the issue was at least discussed in two further trials.

Statistical methods

The statistical methods used are those described by Peto *et al.* (1976), Collins *et al.* (1985) and Yusuf *et al.* (1985) and have been described by Prendiville *et al.* (1988). The trials included in the following overviews have been ranked in order of their methodological 'quality', as assessed in Table 2.

Results

Oxytocin compared with ergot alkaloids (Table 3, Fig. 1a & b)

The seven trials in which oxytocin was compared with ergot alkaloids provide no very strong evidence that these two kinds of oxytocics differ in their effects on the risk of postpartum haemorrhage. In the trial of Vaughan Williams *et al.* (1974) there was no information about postpartum haemorrhage, but the mean blood loss was higher in the ergot alkaloid groups than the oxytocin group. The typical odds ratio derived from the remaining six trials is 0·78 (95% CI 0·56–1·09) and thus suggests that oxytocin is superior. This estimate is heavily influenced by

Table 2. Assessment of methodological quality

Study	Control of selection bias at entry	Control of selection bias after entry	Control of assessment bias
McGinty (1956)	**	***	*
Friedman (1957)	*	*	*
Fugo & Dieckmann (1958)	***	***	***
Barbaro & Smith (1961)	*	***	**
Bonham (1963)	*	***	*
Nieminen & Jarvinen (1963)	*	***	*
Howard *et al.* (1964)	***	***	***
Soiva & Koistinen (1964)	*	*	*
Francis *et al.* (1965*a*)	*	***	**
Francis *et al.* (1965*b*)	***	***	***
Vaughan Williams *et al.* (1974)	**	*	*
Sorbe (1978)	*	***	*
Kerekes & Domokos (1979)	**	***	*
Hacker & Biggs (1979)	*	***	***
Dumoulin (1981)	*	*	*
Docherty & Hooper (1981)	***	***	***
Symes (1984)	**	***	***

Control of selection bias at entry: *** full credit; ** small but real chance of next treatment being discovered by those enrolling; * no attempt at blinding, e g birthdate, patient records, alternate allocation etc.

Control of selection bias after entry. *** primary analysis based on all cases entered; ** analyses after withdrawals too few to engender material bias, question carefully handled; * others

Control of assessment bias: *** blinding successful or irrelevant; ** partially blinded; * no attempt to reduce observer bias

Table 3. Effect of routine oxytocin compared with routine ergot alkaloid administration in the third stage of labour on (a) postpartum haemorrhage (>500 ml or >20 oz) and (b) blood pressure elevation

Study	Oxytocin	Ergot alkaloids	Odds ratio	95% CI
(a) Postpartum haemorrhage				
Howard *et al.* (1964)	15/470	9/493	1·75	0·78–3·94
Fugo & Dieckmann (1958)	0/324	0/149	—	—
McGinty (1956)	0/50	1/100	0·22	0·00–14 26
Nieminen & Jarvinen (1963)	9/689	10/689	0·90	0·36–2·22
Sorbe (1978)	33/506	52/543	0·66	0·43–1·03
Friedman (1957)	4/214	20/503	0·52	0·21–1·27
Typical odds ratio			0·78	0·56–1·09
(b) Blood pressure elevation				
Howard *et al* (1964) (systolic or diastolic >20 mmHg)	69/479	91/504	0·77	0 55–1·07
McGinty (1956) (systolic ⩾20 mmHg)	17/50	26/100	1·47	0·70–3·12
Friedman (1957) (systolic >25 or diastolic >20 mmHg)	0/214	14/503	0 23	0·07–0·74
Typical odds ratio			0·78	0·58–1·06

CI, Confidence interval

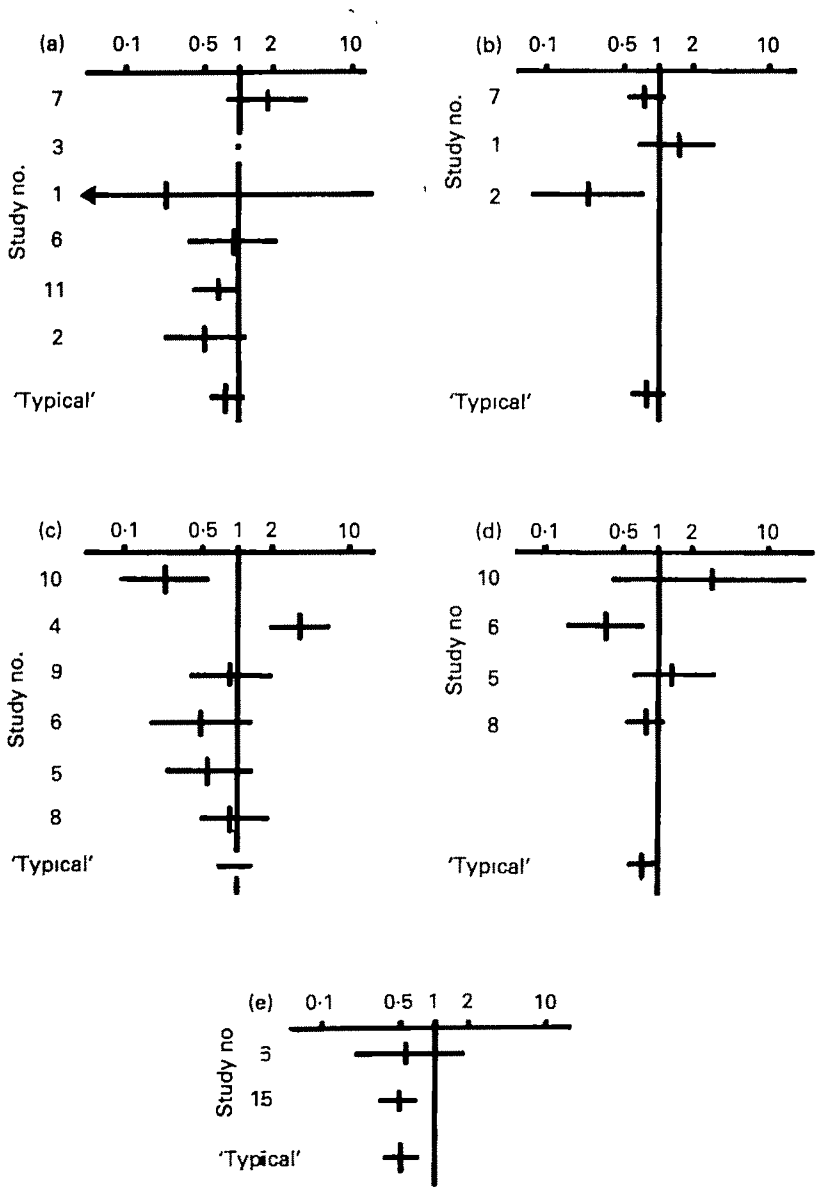

Fig. 1. Effects of oxytocin preparation administered in the third stage of labour (a & b) oxytocin compared with ergot alkaloids (Table 3) on (a) postpartum haemorrhage, (b) blood pressure elevation; (c & d) Syntometrine compared with ergot alkaloids (Table 4) on (c) postpartum haemorrhage, (d) prolonged third stage; (e) Syntometrine compared with oxytocin on postpartum haemorrhage (Table 5). —+— indicates the odds ratio with the 95% confidence interval. The study number codes are listed in Table 1

the two trials in which bias is most likely to have been operating.

In only three of the trials in which the oxytocic was given before the end of the third stage was placental delivery discussed. Although they do not use strictly comparable endpoints, all three suggest that oxytocin is less likely than ergot alkaloids to predispose to delayed placental delivery. Nieminen & Jarvinen (1963) found a greater risk of prolonged third stage (>30 min) and retained placenta in the ergometrine group. Sorbe (1978) also found that oxytocin was less likely than ergot alkaloids to be associated with prolonged third stage, trapped or partially retained placenta and a need for manual removal of the placenta. Fugo & Dieckmann (1958) found no statistically significant differences between the trial arms in terms of the time to 'spontaneous' delivery of the placenta, over 60% being delivered within 3 min of oxytocic administration. Manual removal was performed in a very high proportion however (24% in the ergotrate group and 17% in the oxytocin groups) 'to train residents in this procedure'.

Five of the seven papers provided information on pressor effects. Vaughan Williams *et al.* (1974) showed that oxytocin was less likely than ergometrine to cause a rise in central venous pressure. Fugo & Dieckmann (1958) merely state that there were no significant differences in blood pressure between the groups. A typical odds ratio of 0·78 (95% CI 0·58–1·06) for blood pressure elevation was derived from the only three trials which provided data suitable for meta-analysis. Thus, the available evidence suggests that oxytocin is less likely than ergot alkaloids to cause hypertension.

These three studies also commented on side-effects such as headache, nausea and vomiting Howard *et al.* (1964) and McGinty (1956) reported no differences between women given oxytocin and ergot alkaloids, but Friedman (1957) stated that these effects were significantly worse in the ergot alkaloid than the oxytocin group.

Syntometrine compared with ergot alkaloids alone (Table 4, Fig. 1c & d)

There was no statistically significant difference between Syntometrine and ergot alkaloids in the rate of postpartum haemorrhage in the six trials in which data were available (typical odds ratio 1.02; 95% CI 0·75–1·39). A typical odds ratio of 0·78 (95% CI 0·58–1·04) suggested that Syntometrine was less likely than ergot alkaloids to be associated with a prolonged third stage.

Only Hacker & Biggs (1979) considered blood pressure and they found that Syntometrine was less likely than ergometrine to be associated with a 20 mmHg elevation of diastolic blood pressure.

Table 4. Effect of routine Syntometrine compared with routine ergot alkaloid administration in the third stage of labour on (c) postpartum haemorrhage (>500 ml or >20 oz) and (d) prolonged third stage

Study	Syntometrine	Ergot alkaloids	Odds ratio	95% CI
(c) Postpartum haemorrhage				
Francis *et al.* (1965*b*)	4/171	17/150	0·23	0·10–0·56
Barbaro & Smith (1961)	39/300	10/300	3·62	2·02–6·49
Francis *et al* (1965*a*)	18/587	10/300	0·92	0·41–2·03
Nieminen & Jarvinen (1963)	5/689	10/689	0·51	0·18–1.41
Bonham (1963)	5/391	19/792	0·57	0·24–1·34
Soiva & Koistinen (1964)	18/560	19/560	0·95	0·49–1·82
Typical odds ratio			1 02	0·75–1 39
(d) Prolonged third stage				
Francis *et al.* (1965*b*)	3/171	1/183	2·94	0·41–4·07
Nieminen & Jarvinen (1963)	6/689	19/689	0·35	0 16–0·71
Bonham (1963)	10/391	15/792	1·38	0·59–3 20
Soiva & Koistinen (1964)	66/560	81/560	0·79	0·56–1·12
Typical odds ratio			0·78	0·58–1·04

CI, Confidence interval.

Table 5. Effect of routine Syntometrine compared with routine oxytocin administration in the third stage of labour on postpartum haemorrhage (>500 ml or >20 oz)

Study	Syntometrine	Oxytocin	Odds ratio	95% CI
Nieminen & Jarvinen (1963)	5/689	9/689	0·56	0·20–1·61
Dumoulin (1981)	52/1000	74/750	0·50	0·35–0·72
Typical odds ratio			0·51	0·36–0·71

CI, Confidence interval

Syntometrine compared with oxytocin (Table 5, Fig. 1e)

Both trials giving data on postpartum haemorrhage in which Syntometrine was compared with oxytocin alone suggested that Syntometrine is superior in reducing the risk of postpartum haemorrhage (typical odds ratio 0·50; 95% CI 0·36–0·71). This was reflected in the findings by Docherty & Hooper (1981) and by Dumoulin (1981) of a lower mean blood loss in the Syntometrine group (383 ml *vs* 278 ml; 264 ml *vs* 230 ml respectively). In contrast, Vaughan Williams *et al.* (1974), who did not present data on PPH as such, found a higher mean blood loss in the Syntometrine groups (with or without diazepam) than in the oxytocin group (184 ml *vs* 99 ml).

The length of the third stage was explicitly considered in only one of the trials (Nieminen & Jarvinen 1963). The odds of prolonged third stage (>30 min) were reduced with Syntometrine, although retained placentas were more common after using this preparation. Neither difference was statistically significant. Dumoulin (1981) merely noted that the incidence of manual removal of the placenta did not differ significantly between the two experimental groups.

None of these trials examined blood pressure elevation as an outcome, but Vaughan Williams *et al.* (1974) considered the effects of oxytocics on mean central venous pressure and showed that this was more likely to rise following Syntometrine than after oxytocin used alone. This effect was not detected if women had been given diazepam late in the first stage of labour.

Symes (1984) showed that Syntometrine suppresses serum prolactin levels and that it may therefore have an adverse effect on breast-feeding. As there was no evidence of a comparable effect of oxytocin, he concluded that this was due to the ergot alkaloid component of Syntometrine.

Timing and route of oxytocic administration

Although, as Table 1 demonstrates, there was considerable variation between trials in terms of the timing of oxytocic administration, only Vaughan Williams *et al.* (1974) and Francis *et al.* (1965*b*) explicitly compared timing of a particular drug, ergometrine. In neither trial was any effect of timing of administration identified.

Similarly, although a number of trials (Hacker & Biggs 1979; Kerekes & Domokos 1979; Nieminen & Jarvinen 1963; Soiva & Koistinen 1964; Vaughan Williams *et al.* 1974) compared intravenous ergot alkaloids with other oxytocics given intramuscularly, no trial compared the effect of using different routes for administering the same drug.

Discussion

The evidence presented provides no support for the continued routine use of ergot alkaloids alone in managing the third stage of labour. Not only is there no evidence that they are more effective than other preparations, but they have unwanted side-effects, particularly on blood pressure.

The available evidence (derived from two trials in which bias may well have operated) suggests that prophylactic use of a combination of oxytocin and ergometrine (Syntometrine) is more effective in reducing the risk of postpartum haemorrhage than oxytocin used alone. If indeed Syntometrine does afford greater protection against haemorrhage than oxytocin used alone, this may be at the expense of a greater risk of hypertension.

Despite many anecdotal and case series reports of the effect of prostaglandins or their analogues in controlling postpartum haemorrhage (Tagaki *et al.* 1976, Henson *et al.* 1983; Toppozada *et al.* 1981), only one trial has assessed the efficacy of a prostaglandin used prophylactically (Kerekes & Domokos 1979). Both blood loss and the length of the third stage were reduced when compared with ergometrine (0·2 mg i.v.), but the prostaglandin was administered intramyometrially which reduces considerably its acceptability as a routine preventive measure. If prostaglandins are to be used at all as a routine adjunct in the management of the third stage of labour, they should only be used in the context of randomized trials designed to compare their effects with those of either oxytocin alone or Syntometrine.

Given the marked differences in North American and British practice, a large controlled trial comparing Syntometrine and oxytocin would be informative in obtaining both unbiased and more precise estimates of their relative effects on postpartum haemorrhage, blood pressure and unpleasant symptoms.

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References

Barbaro, C A. & Smith, G. O (1961) Clinical trial of SE505—a new oxytocic mixture *Aust NZ J Obstet Gynaecol* **1**, 147-150

Bonham, D. G. (1963) Intramuscular oxytocics and cord traction in third stage of labour. *Br Med J* **ii**, 1620.

Chalmers, I., Hetherington, J., Newdick, M., Mutch, L., Grant, A., Enkin, M., Enkin, E & Dickersin, K. (1986) A register of controlled trials in perinatal medicine. *Controlled Clin Trials* **7**, 306-324

Chukudebelu, W. O., Marshall, A. T & Chalmers, J A. (1963) Use of 'syntometrine' in the third stage of labour. *Br Med J* **i**, 1390-1391

Collins, R., Yusuf, S & Peto, R. (1985) Overview of randomised trials of diuretics in pregnancy *Br Med J* **290**, 17-23.

Daley, D. (1951) The use of intramuscular ergometrine at the end of the second stage of normal labour. *J Obstet Gynaecol Br Emp* **57**, 388-397.

Dickersin, K., Hewitt, P , Mutch, L , Chalmers, I. & Chalmers, T. C. (1985) Perusing the literature. comparison of MEDLINE searching with a Perinatal Trials Database. *Controlled Clin Trials* **6**, 306-317.

Docherty, P. W. & Hooper, M (1981) Choice of an oxytocic agent for routine use at delivery. *J Obstet Gynaecol* **2**, 60.

Dumoulin, J. G (1981) A reappraisal of the use of ergometrine. *J Obstet Gynaecol* **1**, 178-181

Forster, F. M. C. (1957) A comparative study of ergometrine and 'Methergin' used in the management of the third stage of labour *Med J Aust* **2**, 155-156.

Francis, H. H , Miller, J. M. & Porteous, C R. (1965) Clinical trial of an oxytocin-ergometrine mixture *Aust NZ J Obstet Gynaecol* **5**, 47-51

Friedman, E. A (1957) Comparative clinical evaluation of postpartum oxytocics. *Am J Obstet Gynecol* **73**, 1306-1313.

Fugo, N. W. & Dieckmann, W. J (1958) A comparison of oxytocic drugs in the management of the placental stage. *Am J Obstet Gynecol* **76**, 141-146.

Garcia, J , Garforth, S. & Ayers, S (1987) The policy and practice of midwifery study: introduction and methods. *Midwifery* **3**, 2-9

Groeber, W. R. & Bishop, E. H (1960) Methergine and ergonovine in the third stage of labor. *Obstet Gynecol* **15**, 85-88.

Hacker, N. F. & Biggs, J. S G (1979) Blood pressure changes when uterine stimulants are used after normal delivery. *Br J Obstet Gynaecol* **86**, 633-636

Henson, G., Gough, J. D & Gillmer, M D. G. (1983) Control of persistent primary postpartum haemorrhage due to uterine atony with intravenous prostaglandin E_2. Case report. *Br J Obstet Gynaecol* **90**, 280-282.

Howard, W F., McFadden, P. R. & Keettel, W C. (1964) Oxytocic drugs in fourth stage of labor *JAMA* **189**, 411-413.

Kerekes, L & Domokos, N (1979) The effect of prostaglandin F2-alpha on third stage labour. *Prostaglandins* **18**, 161-166.

McGinty, L. B (1956) A study of the vasopressor effects of oxytocics when used intravenously in the third stage of labour. *West J Surg* **64**, 22-28

Moore, J H. (1956) Is methylergonovine tartrate superior to ergonovine maleate? *Am J Obstet Gynecol* **71**, 908-911.

National Perinatal Epidemiology Unit (1985) *A Classified Bibliography of Controlled Trials in Perinatal Medicine 1940–1984* Oxford University Press, Oxford.

Nelson, G. H. (1983) Use of 15-methyl prostaglandin F2-alpha postpartum to contract the uterus in normal pregnant women. *J Med Assoc Ga* **72**, 703-706.

Newton, M , Mosey, L M , Egli, G E , Gifford, W B. & Hull, C. T (1961) Blood loss during and immediately after delivery. *Obstet Gynecol* **17**, 9-18.

Nieminen, U. & Jarvinen, P A. (1963) A comparative study of different medical treatments of the third stage of labour *Ann Chir Gynaecol Fenn* **53,** 424-429.

Paull, J. D. & Ratten, G. J. (1977) Ergometrine and third stage blood loss. *Med J Aust* **1,** 178-179.

Peto, R., Pike, M. C., Armitage, P. *et al* (1976) Design and analysis of randomised clinical trials requiring prolonged observation of each patient I. Introduction and design. *Br J Cancer* **34,** 585-612.

Prendiville, W., Elbourne, D & Chalmers, I. (1988) The effects of routine oxytocic administration in the management of the third stage of labour an overview of the evidence from controlled trials. *Br J Obstet Gynaecol* **95,** 3-16.

Rooney, I., Hughes, P. & Calder, A. (1985) Is routine administration of syntometrine still justified in the management of the third stage of labour? *Health Bull* **43/3,** 99-101

Soiva, K & Koistinen, U. (1964) Clinical experience with simultaneous intramuscular injection of oxytocin and methylergometrine *Ann Chir Gynaecol* **53,** 173-186.

Sorbe, B. (1978) Active pharmacologic management of the third stage of labour *Obstet Gynecol* **52,** 694-697.

Stearn, R. H (1963) Syntometrine in the management of the third stage of labour *J Obstet Gynaecol Br Commonw* **70,** 593-596.

Symes, J B. (1984) A study on the effect of ergometrine on serum prolactin levels following delivery. *J Obstet Gynaecol* **5,** 36-38

Tagaki, S , Yoshida, T. & Togo, Y. (1976) The effects of intramyometrial injections of prostaglandin PGF_2 on severe postpartum haemorrhage. *Prostaglandins* **12,** 565-579.

Toppozada, M., El-Bossati, M., El Rahman, H A. & Shams et-Din, A. H. (1981) Control of intractable atonic postpartum haemorrhage by 15-methyl prostaglandin F_2 *Obstet Gynecol* **58,** 327.

Vaughan Williams, C., Johnson, A. & Ledward, R (1974) A comparison of central venous pressure changes in the third stage of labour following oxytocic drugs and diazepam. *J Obstet Gynaecol Br Commonw* **81,** 596-599.

Yusuf, S., Peto, R., Lewis, T , Collins, R. & Sleight, P. (1985) Beta blockade during and after myocardial infarction: an overview of the randomised trials. *Prog Cardiovasc Dis* **XXVII, 5,** 336-371.

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Magnetic resonance imaging (MRI) in obstetrics. I. Maternal anatomy

M. C. POWELL, B. S. WORTHINGTON, J. M. BUCKLEY, E. M. SYMONDS

Summary. We assessed the ability of magnetic resonance, a recently introduced imaging technique, to demonstrate the maternal anatomy in obstetrics. The signal intensity of different maternal tissues using T_1 and T_2 weighted sequences was examined. The bony pelvis is depicted with sufficient clarity to provide an alternative to conventional X-ray pelvimetry. The placenta and cervix have a distinctive appearance facilitating the diagnosis of placenta praevia. The unique demonstration of cervical morphology will offer the potential for investigation into the ill-understood conditions of cervical dystocia and cervical incompetence.

The introduction of ultrasound in the 1960s is considered a milestone in the development of modern obstetrics (Donald 1965). Arterial placentography, amniography and fetography have since become obsolete. The technique has limitations, however, ranging from its dependence on operator skill and patient habitus to its poor ability to characterize tissues. In addition, depiction of the maternal deep pelvis and the structures within may be especially difficult.

Magnetic resonance is a recently introduced imaging technique which is an appealing alternative. It employs radiofrequency radiation in the presence of a magnetic field to produce cross-sectional images of the body. The images are essentially distribution density maps of protons and their related parameters (the so-called T_1 and T_2 times) in lipid and water.

Prototype clinical MR imaging systems were first set up in Nottingham, Aberdeen and London. The first obstetric images (Fig. 1) produced by the Aberdeen and Nottingham units were promising, despite limitations in their spatial resolution and soft tissue contrast (Smith *et al.* 1983; Johnson *et al.* 1984). Subsequent technical advances have been rapid and now the place of MRI in the musculoskeletal system and central nervous system is established (Worthington 1983). Unlike the upper abdomen, pelvic imaging is not degraded by movement arising from respiration or peristalsis. The role of MRI in obstetrics is still to be assessed. We present our initial experience with 154 women so far examined.

Subjects and methods

In Nottingham, MRI is performed on a Picker 0·15T system based on a resistive magnet. Single slice and multislice protocols are available, in transverse axial, coronal or sagittal planes. By altering the pattern of radiofrequency waves applied to the pulse sequences images can be produced weighted by T_1 or T_2. T_2 weighted pulse sequences (spin echo) gave both good tissue differentiation and good resolution. The T_1 weighted sequences (inversion recovery) used in our study gave useful pathological information but were associated with a higher noise level. The pulse sequences and their image weighting are given in Table 1. Imaging time

University Hospital, Queen's Medical Centre, Nottingham
Department of Obstetrics and Gynaecology
M. C. POWELL
E. M. SYMONDS

Department of Diagnostic Radiology
B. S. WORTHINGTON
J. M. BUCKLEY

Correspondence: Mr M. C. Powell, Birthright Research Fellow, Department of Obstetrics and Gynaecology, University Hospital, Queen's Medical Centre, Nottingham NG7 2UH

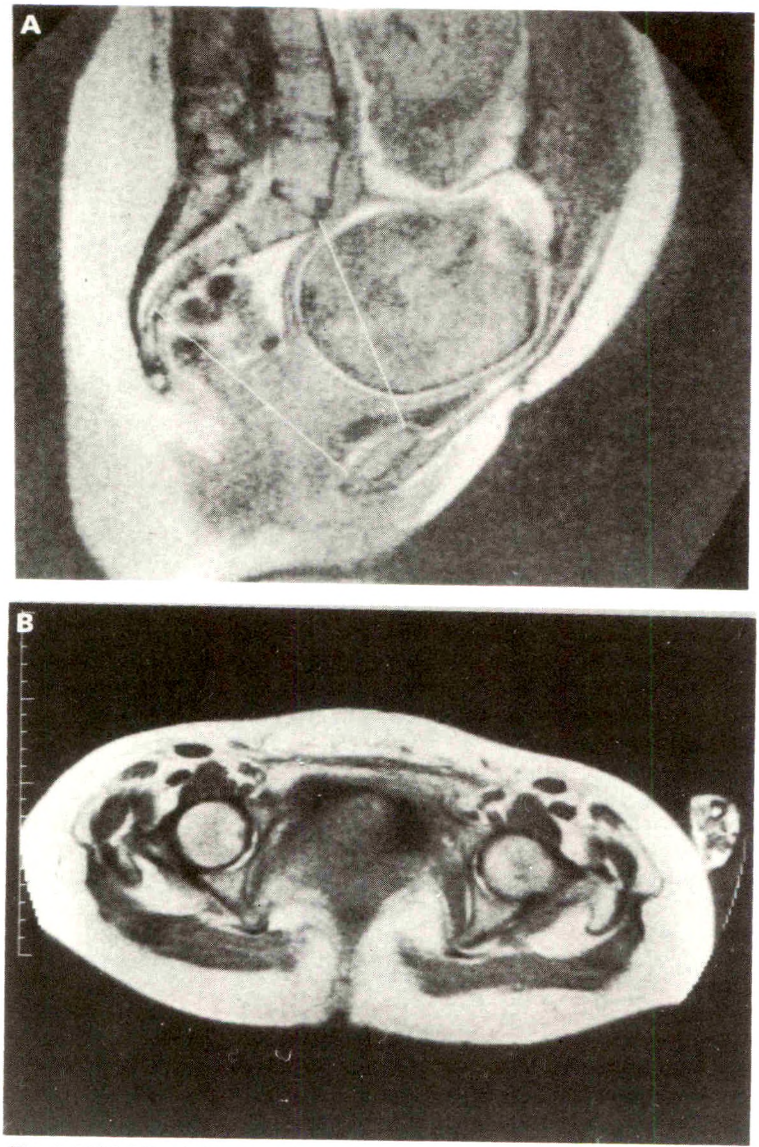

Fig. 1. (A) MRI pelvimetry at 36 weeks gestation. API and APO measurements. Cephalic presentation (TR 500 ms, TE 40 ms). (B) Transverse axial scan through ischial spines for bispinous measurement (TR 500 ms, TE 40 ms).

depends on the pulse sequence employed and the level of resolution required. Images are acquired and displayed on a 256 × 256 matrix yielding a pixel size of 0·8 cm and a slice thickness of 1 cm.

Guidelines for the use of magnetic resonance imaging have been laid down by the National Radiological Protection Board (1983). Although no genotoxic or oncogenic potential has been found (Cooke & Morris 1981; Thomas & Morris 1981), it advises against imaging in the first trimester during the period of rapid organogenesis. In addition, in Nottingham, examinations address specific clinical problems or situations where ultrasound has known limitations. The maternal indications for MRI examination in our studies are listed in Table 2. All studies have been approved by the local ethics committee. Informed consent was obtained before examination in each case.

Results

In all the women examined maternal anatomy was demonstrated with good resolution.

Table 1. Available magnetic resonance imaging (MRI) sequences

Sequence	Image weighting
Spin echo with short repetition time (TR) and short echo delay time (TE)	$T_1 + T_2$
Spin echo with long TR and long TE	T_2
Inversion recovery with medium or long inversion time (TI)	T_1

Table 2. Maternal indications for MRI examination

Placental abruption	16
Unstable lie	3
Placenta praevia	75
Pelvimetry	46
Gestational trophoblastic neoplasia	12
Concurrent pelvic mass	2
Total	154

The bony pelvis

X-ray pelvimetry now represents the major source of ionizing radiation to which the fetus is exposed. The potential hazardous side-effects from irradiation in pregnancy are well documented (Stewart *et al.* 1956). Therefore MRI has been investigated as an alternative in the measurement of pelvic diameters.

Figures 1A and B are sagittal and transverse axial scans of a 36-week pregnancy with a cephalic presentation. Cortical bone is represented as a low intensity line. Measurements are taken from the edge of this line with the computer cursor. A four-slice, transverse axial protocol demonstrates the ischial spine and calculation of the bispinous diameter is performed in a similar manner to above. In a study of 28 patients who had both X-ray and MRI pelvimetry a good concordance between the results was found (Powell *et al.* 1985). Scanning times are similar with the MRI examination lasting 10 min. Due to field inhomogeneties which could induce geometric distortion, we have found it necessary to image a copper sulphate phantom of known dimensions before an MRI examination to determine any correction factor which may be required.

Some variation occurred between the X-ray and MRI results in the anteroposterior inlet and outlet measurements. This, we believe, is related to patient posture during the examin-

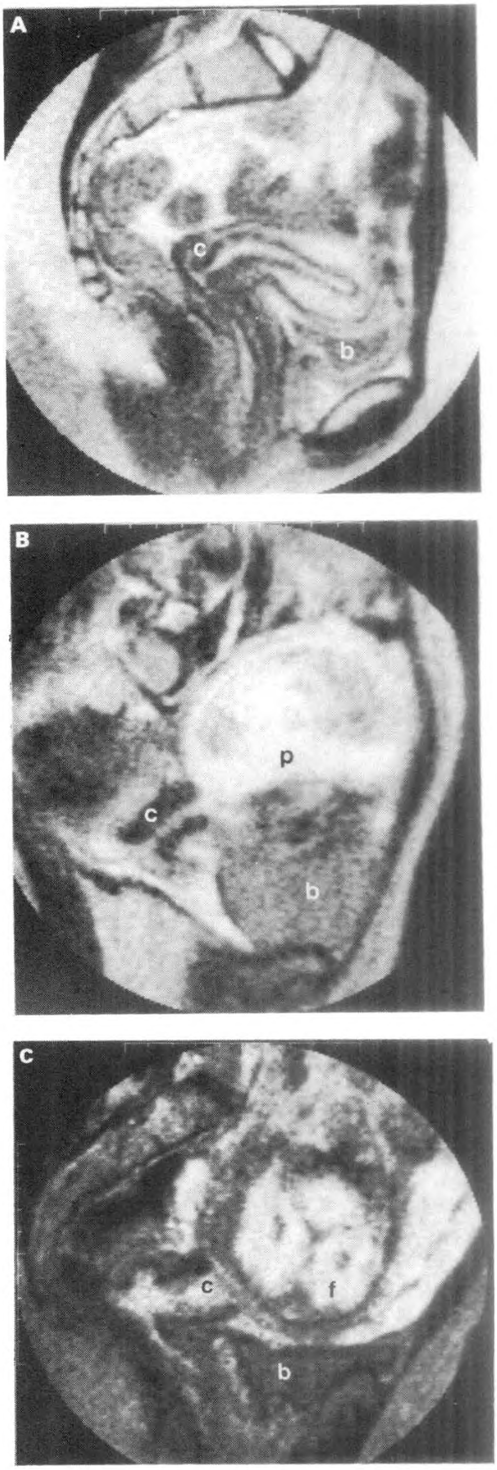

Fig. 2. The cervix (c) (TR 2000 ms, TE 80 ms). (A) Non-pregnant; (B) At 12 weeks gestation, placenta (p); (C) At 37 weeks, 1 cm dilated, fetal cerebral cortex (f), bladder (b).

ation being supine with MRI and erect for an X-ray. This variance may be up to 2 cm and was initially observed by Russell (1969) in his assessment of X-ray pelvimetry.

The cervix

Ultrasound assessment of the cervix is generally accepted to be of limited value. Over-distension of the maternal bladder and acoustic shadowing from the fetal head may preclude display of the cervix, or lead to a false impression of its length (Goldberg 1983). The internal structure of the cervix is not discernible. MRI offers a unique method for examining the internal architecture of the cervix and of the complex changes it undergoes during pregnancy. The cervix has a characteristic appearance both in the non-pregnant and the pregnant state (Figs 2A, B & C). This appearance is unique to MRI and cannot be seen with other imaging techniques. A band of low intensity is visible on either side of the cervical canal. The mucus within the canal has a high signal intensity with this T_2 weighted sequence. As yet, the nature of the low intensity band of the cervix is unknown, it is our belief that this may have a collagenous origin (Worthington *et al.* 1985). MRI may offer a potential insight into the ill-understood conditions of cervical dystocia and cervical incompetence.

The placenta

The placental site is well demonstrated with MRI because of the high signal intensity that is obtained when long T_2 weighted sequences are employed (Fig. 3). Ultrasound has an accuracy of over 90% in the detection of a placenta praevia (Edelstone 1977). Inaccuracies occur in particular relation to the posteriorly situated placenta praevia which is difficult to detect with certainty (Scheer 1973). False positives may lead to unnecessary hospitalization and surgery (Gorodeski *et al.* 1982). In a study involving 25 women with ultrasound diagnoses of a placenta praevia who were also investigated with MRI, the degree of placenta praevia was over-estimated in seven and the subsequent MR scan

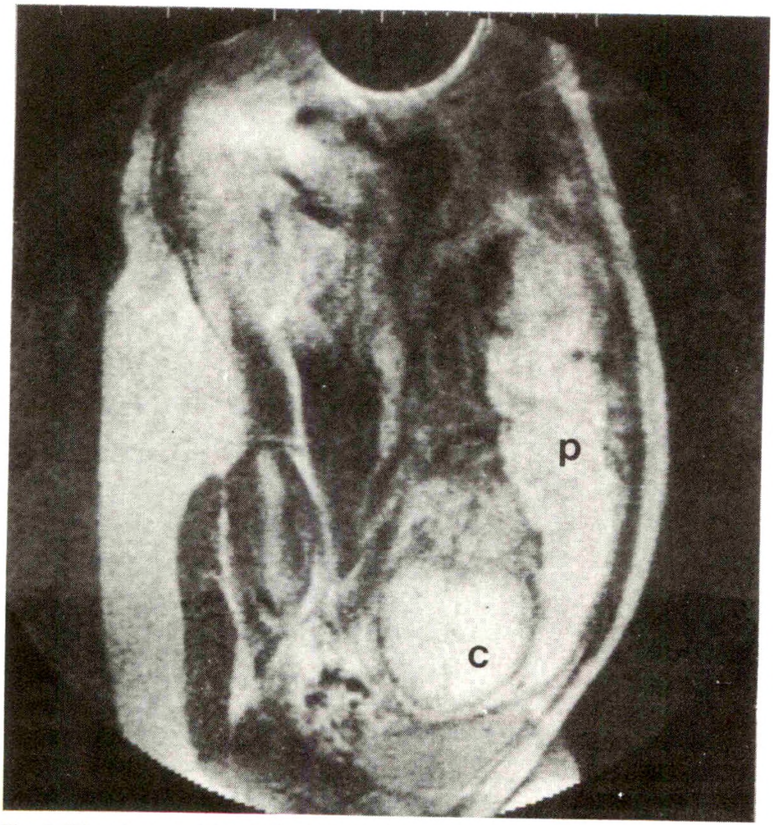

Fig. 3. The placenta (p), cerebral cortex (c) (TR 2000 ms, TE 80 ms).

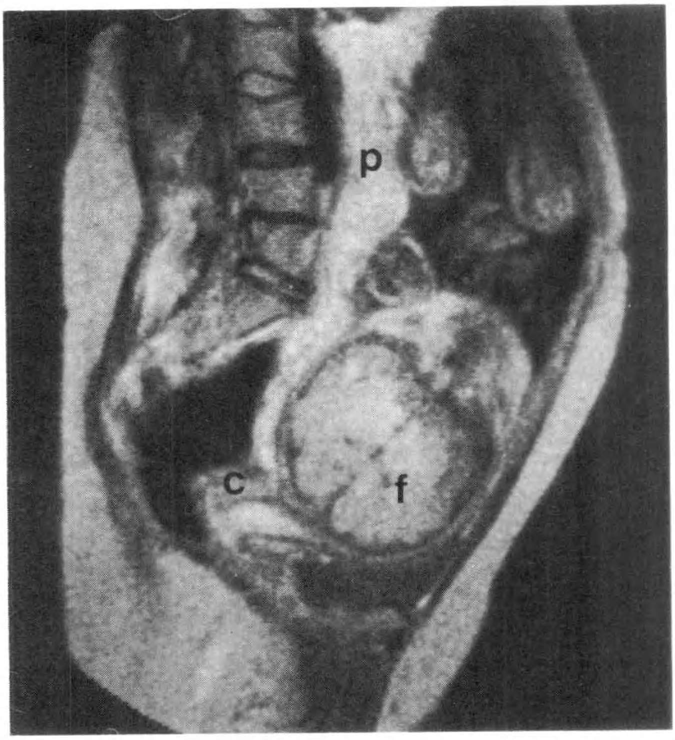

Fig. 4. Marginal placenta praevia, placenta (p), cervix (c), fetal cerebral cortex (f) (TR 1000 ms, TE 80 ms).

enabled the clinician to reduce their length of stay in hospital and in one patient avoid what would have been an unnecessary caesarean section (Powell *et al.* 1986*a*). With MRI, because of the easy identification of the cervix and placenta, the relation of the placental lower edge to the internal os can be precisely stated (Fig. 4). This is best demonstrated using sagittal images, but coronal and transverse axial views may be necessary.

The diagnosis of placental abruption is important because of the associated maternal and fetal morbidity and mortality (Donald 1977). Ultrasound examination is of limited value in the diagnosis of the revealed abruption (Gottesfeld 1984). The MRI characteristics of acute and chronic extracranial haemorrhage have been studied (Unger *et al.* 1986). A high signal intensity is associated with haemorrhage when a T_1 weighted pulse sequence is employed. This has led us to believe MRI may have a place in the diagnosis of placental abruption. Unfortunately, the high signal intensity of the haemorrhage only occurs after 48 h. This is related to the shortening of the T_1 relaxation time, which in part is due to increasing concentration of methaemoglobin (Bradley & Waluch 1985). Therefore at the present time reliable identification of acute haematomas cannot be achieved. Work is continuing in an effort to devise suitable pulse sequences which would allow this to be done.

Pelvic masses in pregnancy

Identification of a pelvic mass occurring in the pregnant patient may present some diagnostic difficulties. Ultrasound is limited by its lack of specificity and there is a natural reluctance to expose the fetus to ionizing radiation. The potential of MRI in the assessment of a pelvic mass has been addressed and found to be superior to other imaging techniques (Hricak *et al.* 1983; Powell *et al.* 1986*b*) in differentiating the origin and nature of a pelvic mass. Figure 5 is a sagittal T_1 weighted scan of a sacral teratoma which was identified at 24 weeks gestation. The MR scan demonstrated the tumour to be retroperitoneal and this was excised after abdominal delivery at 36 weeks and its nature confirmed.

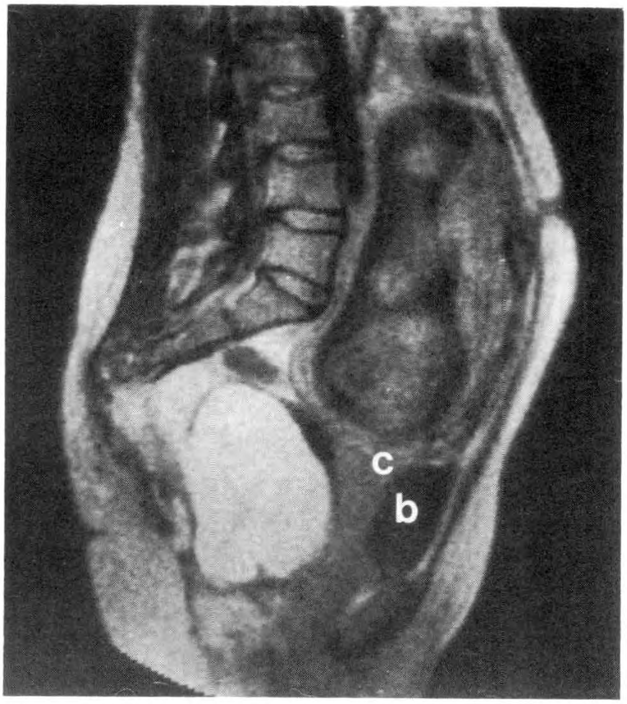

Fig. 5. Sagittal scan at 21 weeks. Large sacral teratoma below uterus, encroaching onto cervix (c), bladder (b) (TR 795 ms, TE 40 ms).

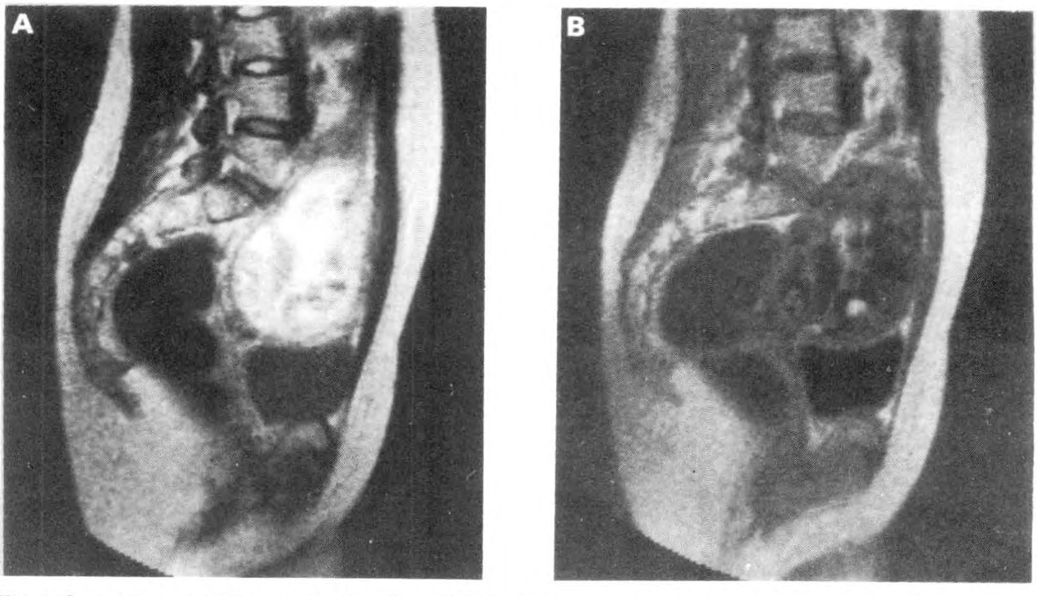

Fig. 6. Complete hydatidiform mole. (A) TR 2000, TE 80 ms (T_2 weighted); (B) TR 2000, TI 600 ms (T_1 weighted).

Gestational trophoblastic neoplasia

Gestational trophoblastic neoplasia occurs in 1 in 1500 pregnancies and the diagnosis is usually readily made with ultrasound. Gestational trophoblastic neoplasia, as seen with MRI, also has a distinctive appearance (Figs 6A & B). On T_2 weighted sequences the molar tissue has a high signal intensity comparable to that of placenta. T_1 weighted sequences demonstrate that this tissue is composed of two parts. The low signal represents trophoblastic tissue and anteriorly a high signal area representing blood. The high specificity of MRI for trophoblastic disease has led us to believe that this will be a useful technique for the detection of recurrent trophoblastic disease when rising human chorionic gonadotrophin titres are found (Powell *et al.* 1986*c*). MRI may also be used to assess the response of the tumour to chemotherapy.

Discussion

Although recent papers have assessed the potential for MRI in obstetrics (Smith *et al.* 1985; Johnson *et al.* 1984), their images have been achieved with prototype clinical systems which provided limited pulse sequences and poor resolution. On a commercial resistive magnet system with a wider range of pulse sequences available, MRI is capable of accurate depiction of the maternal anatomy and can provide a unique insight into cervical and placental morphology. There is no doubt that because of its relative low cost and flexibility ultrasound will remain an integral part of antenatal care. MRI will act as a useful adjunct in situations where ultrasound has known limitations and will make an important contribution to obstetric research.

References

Bradley, W. G. & Waluch, V. (1985) Blood flow: magnetic resonance imaging. *Radiology* **154,** 443-450.

Cooke, P. & Morris, P. G. (1981) The effects of NMR exposure on living organisms. II. A genetic study of human lymphocytes. *Br J Radiol* **54,** 622-625.

Donald, I (1965) Ultrasonic echo sounding in obstetrical and gynaecological diagnosis *Am J Obstet Gynecol* **93,** 935-941.

Donald, I. (1977) Antepartum haemorrhage. In *Practical Obstetric Problems*, 5th edn, Lloyd-Luke, London, pp. 420-479.

Edelstone, D. I. (1977) Placental localization by ultrasound. *Clin Obstet Gynecol* **20,** 285-296.

Goldberg, B B. (1983) The identification of placenta praevia. *Radiology* **128,** 255-256.

Gorodeski, I. G., Neri, A. & Haimovich, C. M. (1982) Placenta praevia: the ultrasonographic placental localization and its influence on the mode of delivery. *J Reprod Med* **27,** 655-657

Gottesfeld, K. R. (1984) The clinical role of placental imaging. *Clin Obstet Gynecol* **27,** 327-341.

Hricak, H., Alpers, C., Crooks, L E. & Sheldon, P. E (1983) Magnetic resonance imaging of the female pelvis—initial experience. *AJR* **141,** 1119-1128.

Johnson, I. R., Symonds, E. M., Worthington, B S., Broughton Pipkin, F., Hawkes, R. C & Gyngell, M. (1984) Imaging the pregnant human uterus with nuclear magnetic resonance. *Am J Obstet Gynecol* **148,** 1136-1139.

National Radiological Protection Board (NRPB) (1983) Revised guidance on acceptable limits of exposure during nuclear magnetic resonance clinical imaging. *Br J Radiol* **56,** 974-977.

Powell, M. C., Worthington, B. S., Buckley, J. & Symonds, E. M. (1985) Magnetic resonance imaging (MRI) and pelvimetry (abstract). 71st Scientific Assembly of the Radiological Society of North America. **157(P),** 190

Powell, M. C., Buckley, J , Price, M., Worthington, B. S. & Symonds, E M. (1986*a*) Magnetic resonance imaging (MRI) and placenta praevia *Am J Obstet Gynecol* **154,** 565-569

Powell, M. C., Worthington, B. S. & Symonds, E. M (1986*b*) The application of MRI to gynaecology. *Br J Hosp Med* **35(6),** 393-403.

Powell, M. C., Buckley, J., Symonds, E. M & Worthington, B. S. (1986*c*) Magnetic resonance imaging (MRI) and hydatidiform mole. *Br J Radiol* **59,** 561-564.

Russell, J. G. B. (1969) Moulding of the pelvic outlet *J Obstet Gynaecol Br Commonw* **76,** 817-820.

Scheer, K. (1973) Ultrasonic diagnosis of placenta praevia. *Obstet Gynecol* **42,** 707-710.

Smith, F. W., Adam, A & Phillips, W. (1983) NMR imaging in pregnancy. *Lancet* **i,** 61-62

Smith, F. W., Kent, C., Abramovich, D R. & Sutherland, H. W. (1985) Nuclear magnetic resonance imaging—a new look at the fetus. *Br J Obstet Gynaecol* **92,** 1024-1033

Stewart, A., Webb, J., Giles, D. & Hewitt, D. (1956) Malignant disease in childhood and diagnostic irradiation *in utero* *Lancet* **ii,** 447-457

Thomas, A. & Morris, P. G. (1981) The effects of NMR exposure on living organisms. I. A microbial assay. *Br J Radiol* **54,** 615-621

Unger, E. C., Glazer, H S., Lee, J. K. & Ling, D. (1986) MRI of extra cranial haematomas: preliminary observations. *AJR* **146,** 403-407

Worthington, B. S. (1983) Clinical prospects for nuclear magnetic resonance. *Clin Radiol* **34,** 3-12

Worthington, B. S., Powell, M. C., Womack, C., Buckley, J. & Symonds, E M. (1985) The low intensity band on spin-echo images of the uterus: an anatomical and clinico-pathological study (abstract) *Radiology* **157(P),** 320.

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Magnetic resonance imaging (MRI) in obstetrics. II. Fetal anatomy

M. C. POWELL, B. S. WORTHINGTON, J. M. BUCKLEY, E. M. SYMONDS

Summary. Magnetic resonance imaging (MRI) was performed in 36 patients at between 10 and 38 weeks gestation to determine the fetal anatomy that could be identified at different gestations. Fetal motion significantly degraded the image quality in the first and second trimesters, but in the final trimester fetal anatomy was clearly demonstrated. T_2 weighted sequences showed the fetal brain and lungs to have a high signal intensity. Shorter TR leading to a T_1 weighting gave better resolution of the overall anatomy. MRI has revealed the potential for assessment of lung maturity and the growth-retarded fetus.

Magnetic resonance imaging (MRI) because of its lack of known biological hazard may prove to be a useful, non-invasive technique for examination of the fetus. First reports have suggested that it will play a significant role in the assessment of the at-risk fetus (Smith *et al.* 1985; Johnson *et al.* 1984). An alternative non-invasive imaging technique to ultrasound would be of benefit in specific situations where ultrasound has known limitations. We report our experience to date with MRI and the fetus using a commercial resistive MR unit.

Subjects and methods

The indications for an MRI in the 36 patients included in this study are given in Table 1. Imaging was performed on a 0·15T resistive system, within the guidelines laid down by the National Radiological Protection Board (1983). T_1 and T_2 pulse sequences were available for assessment with multiplanar imaging and the optimum sequences for fetal examination were determined. Imaging time is dependent on the TR employed within the pulse sequences and varied from 5 to 45 min. Examinations are performed with the patient on her left side. No adverse effects were encountered during the imaging period except mild claustrophobic feelings initially. Informed consent was obtained before an examination in each case. In addition, ten women entered the study who were to undergo an elective termination in the first trimester. Interpretation of the MRI scan was made with the knowledge of the clinical history and the ultrasound findings. The fetal anatomy identifiable with MRI at different gestations was recorded, and the potential benefits of an MRI examination at these stages were assessed.

Results

Magnetic resonance imaging acquires data over a time interval dependent on the repetition time of the pulse sequence chosen, and to a lesser extent the T_2 or T_1. The technique is not in real time and therefore movement occurring during the scanning period will significantly degrade the image quality. Gating techniques have been suc-

University Hospital, Queen's Medical Centre, Nottingham
Department of Obstetrics and Gynaecology
M. C. POWELL
E. M. SYMONDS

Department of Diagnostic Radiology
B. S. WORTHINGTON
J. M. BUCKLEY

Correspondence: Mr M. C. Powell, Birthright Research Fellow, Department of Obstetrics and Gynaecology, University Hospital, Queen's Medical Centre, Nottingham NG7 2UH

Table 1. Fetal indications for MRI examination

Fetal abnormalities	6
Diabetes	2
Poor fetal growth	18
First trimester termination	10
Total	36

cessfully applied for both respiratory and cardiac imaging (Steiner 1984), but the movement of the fetus *in utero* is random and cannot be overcome by these methods. This therefore restricts the value considerably of MRI in the examination of the fetus in the first and second trimesters, and in our experience we have not found this to be of value.

Fetal movement is significantly reduced during the final trimester and is restricted mainly to the limbs. At this stage detailed observations of the fetal anatomy are possible, utilizing the

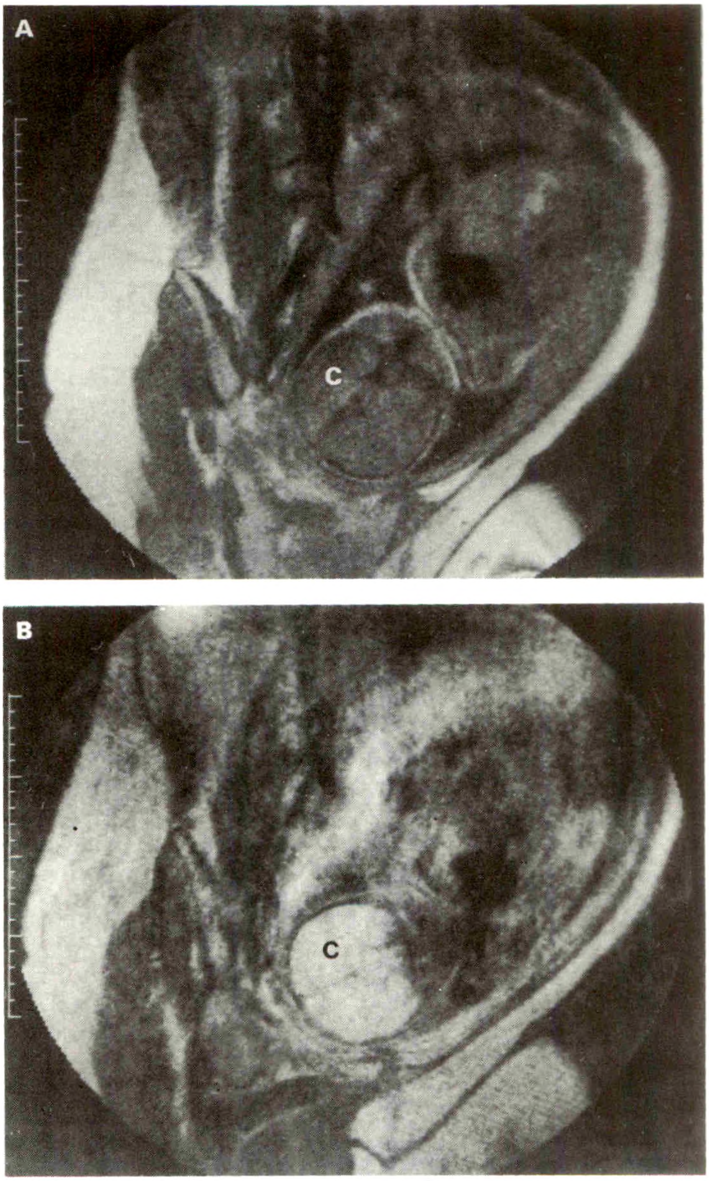

Fig. 1. Fetal cerebral cortex (c) at 33 weeks. (A) TR 500 ms, T_2 40 ms; (B) TR 1000 ms, T_2 80 ms.

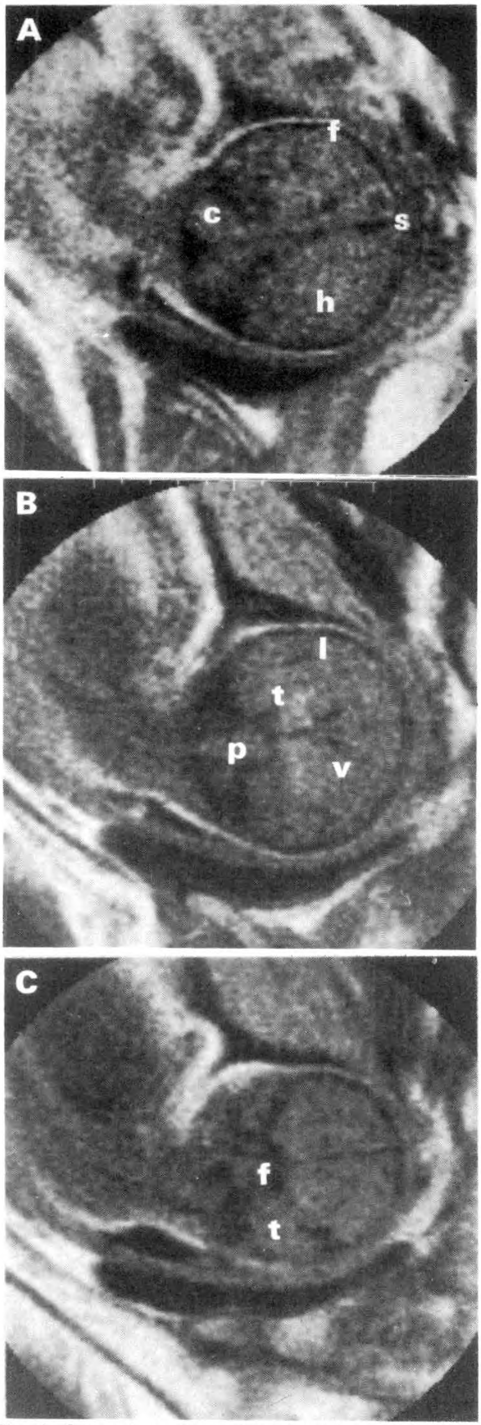

Fig. 2. Coronal sections of the fetal brain. (A) Cerebellum (c), superior sagittal sinus (s), CSF (f), cerebral hemispheres (h); (B) Lateral ventricles (v), third ventricle (t), pons (p), lateral cerebral fissure (l), thalamus with early myelination. TR 500 ms, T_2 40 ms; (C) Temporal lobe (t), frontal sinus (f).

tissue differentiation qualities of MRI, in conjunction with good anatomical resolution.

Central nervous system

The central nervous system has been the principal area of interest in MRI since the first paper describing its application to cerebral abnormalities (Hawkes *et al.* 1980). Subsequent studies have demonstrated its sensitivity to a wide variety of cranial pathology (Bydder *et al.* 1982). The use of MRI in imaging the neonatal brain has also been documented (Johnson *et al.* 1983). MRI may also be a useful technique for examination of the fetal brain, as the fetal central nervous system is well demonstrated in the final trimester of pregnancy.

As in the adult, the signal intensity of the cerebral cortex heightens as the T_2 weighting increases (Fig. 1A & B). On T_2 weighted sequences the fetal brain is identifiable because of its high intensity visible from early in the second trimester. Cerebrospinal fluid within the ventricular system possesses a low signal. This acts as a contrast to the high signal from the cortex. Figures 2A, B and C are coronal sections through the fetal brain using a T_2 pulse sequence with a short repetition time. The cerebellum and spinal cord can be seen. The fetal ventricular system may also be identifiable. The fetal orbit with the non-myelinated optic nerve with a low signal is seen surrounded by the high signal of the orbital fat (Fig. 3). In the adult T_1 weighted pulse sequences provide a distinct contrast between the white matter with a short T_1 relaxation time, and the grey matter. In contradistinction T_1 weighted images of the fetal brain are uniformly featureless (Fig. 4). This would indicate that the cerebral cortex has a long T_1 relaxation time, which is consistent with the known high water content of the fetal brain: 90% in the 10–34 week fetus compared to 72% in a child of 2 years (Larroche 1977; Dobbings & Sands 1973). As the water content of the developing fetal brain falls, so the lipid content rises. Myelination is responsible for the grey–white matter discrimination seen in the adult brain, as this acts to shorten the relaxation time of the white matter. Myelination begins in mid-gestation and continues into the second decade (Yakolev & Lecours 1967). Myelination in the thalami and posterior internal capsule is apparent at 36 weeks to the naked eye and has been seen by MRI in the newborn infant at 40 weeks (Johnson

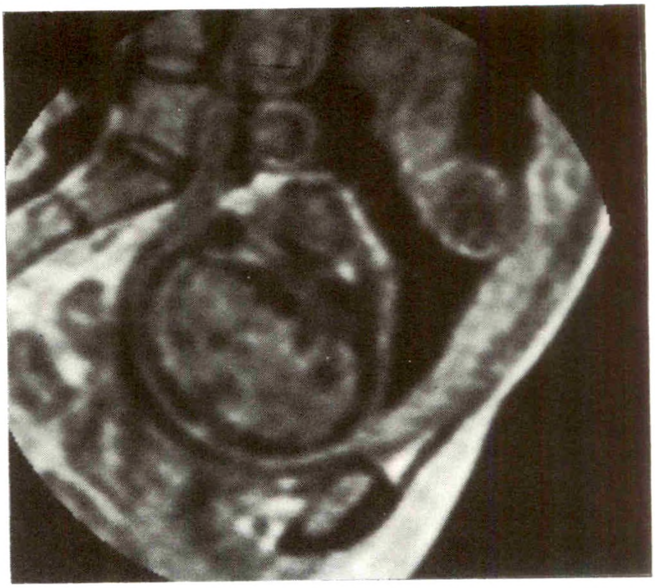

Fig. 3. The fetal orbit. TR 1000 ms, T_2 40 ms.

et al. 1983). In Fig. 2B an area of increased signal due to a shortened T_1 relaxation time of these tissues represents early myelination. Magnetic resonance is the only technique that can display *in utero* the process of physiological myelination. This therefore may offer the potential for recognition of delays or deficits that may occur in its development.

The respiratory system

The fetal lung as seen by MRI has a quite distinct appearance only apparent with this technique (Fig. 5). The characteristic shape facilitates its location, and when T_2 weighted sequences are employed has a high signal intensity. This distinguishes the lungs from the central low inten-

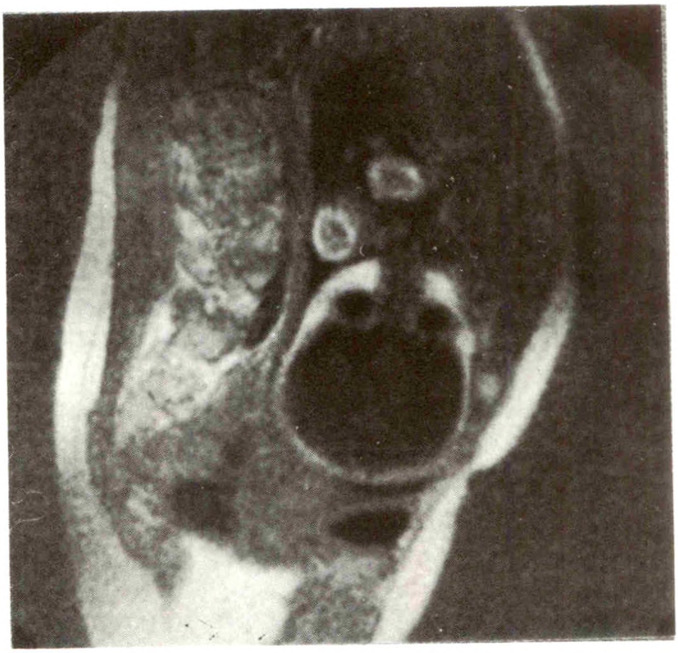

Fig. 4. T_1 weighted transverse section of fetal brain. TR 2000 ms, T_1 600 ms.

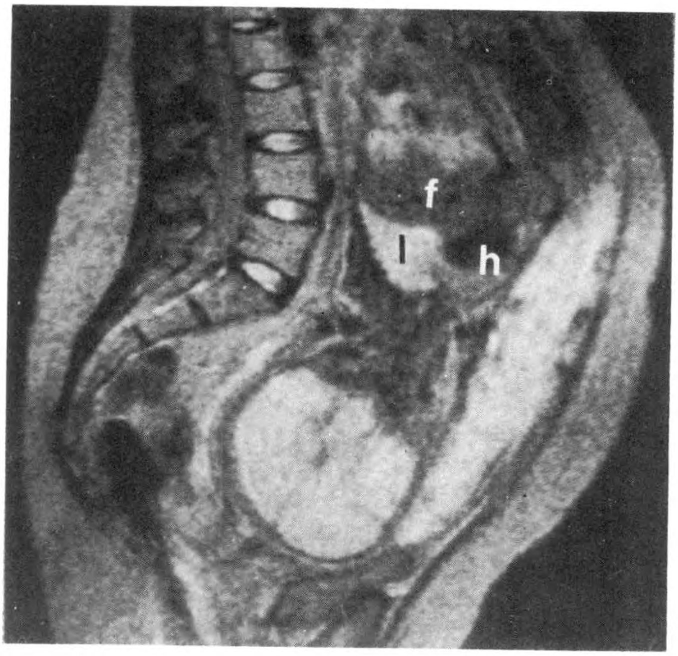

Fig. 5. Fetal lung (l) at 38 weeks. Fetal heart (h), fetal liver (f). TR 2000 ms, T_2 80 ms.

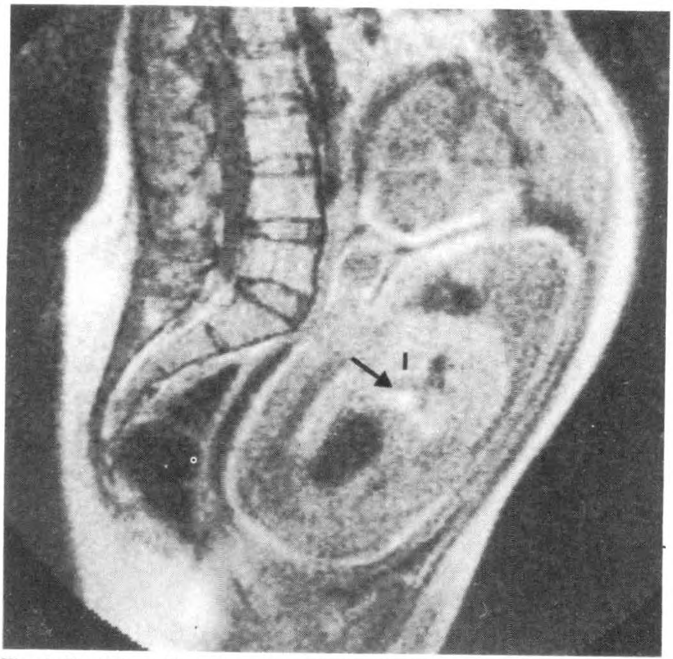

Fig. 6. Fetal liver (l) at 36 weeks, umbilical vein (→). TR 500 ms, T_2 40 ms.

sity area representing the fetal heart. Maturation of the lung commences around 24 weeks gestation (Possmayer 1982). As the lung develops there is an increase in water content and a rise in the phospholipid concentrations that relate to surfactant production (Thieme *et al.* 1983). This would result in a shortening of both the T_1 and T_2 relaxation times of the lung tissue. Respiratory distress syndrome secondary to pulmonary immaturity is a major cause of

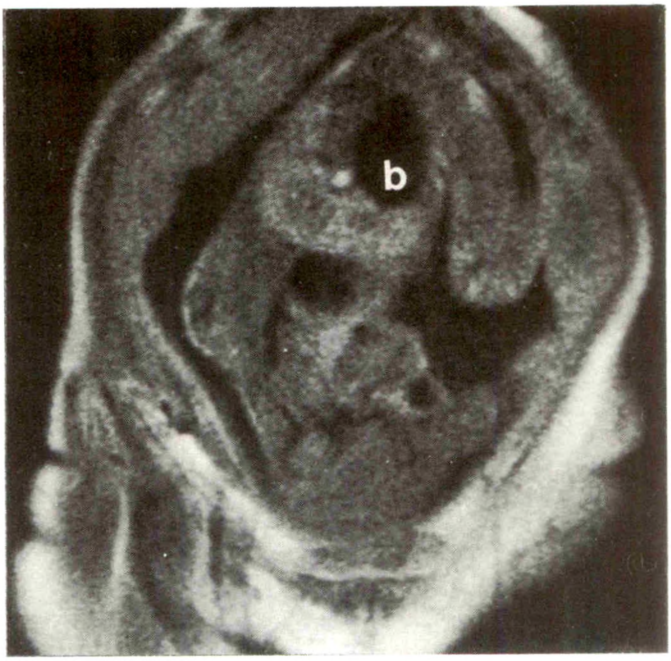

Fig. 7. Fetal bladder (b) at 36 weeks, coronal view. TR 600 ms, T_2 40 ms.

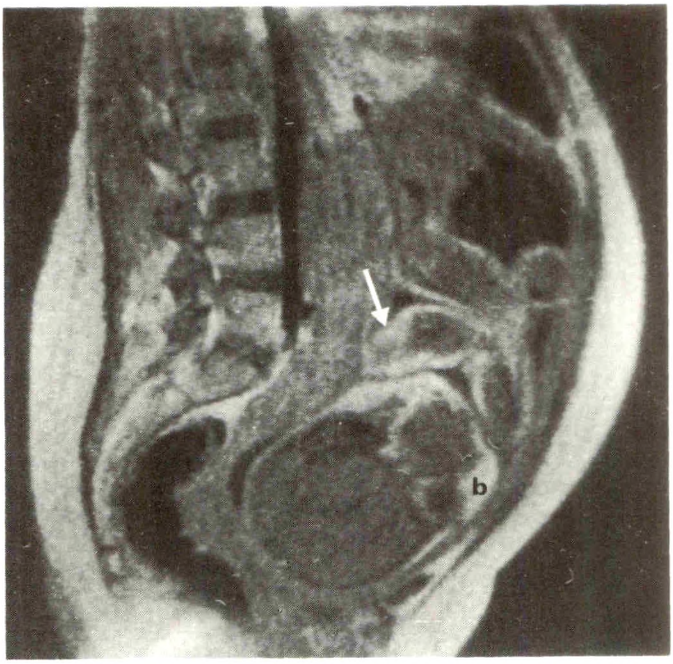

Fig. 8. Fetal subcutaneous fat (→), buccal fat pad (b). TR 500 ms, T_2 40 ms.

morbidity and mortality in premature infants. Assessment of the pulmonary maturity by consideration of the biparietal diameter, placental grading and the appearance of the fetal lung as assessed by echogenicity, texture and through transmission with ultrasonic techniques have proved to be unreliable (Cayea *et al.* 1985; Hadlock *et al.* 1985). The most sensitive prenatal indicator of pulmonary maturity is the lecithin/sphingomyelin ratio in the amniotic fluid which requires an amniocentesis (Hallman & Teramo 1981). This may be difficult in cases associated

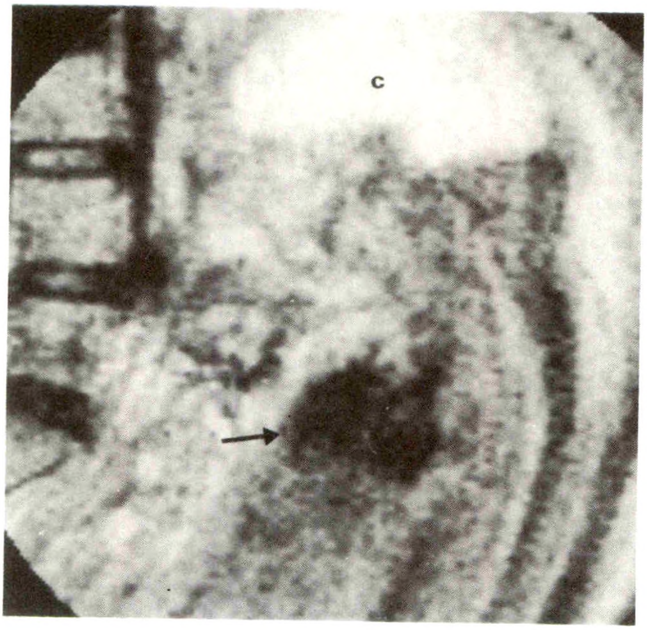

Fig. 9. Fetal cardiac image—left and right chambers (→) cerebral cortex (c). TR 2000 ms, T_2 80 ms.

with severe oligohydramnios. MRI may well present a non-invasive method of determining lung maturity, by assessment of signal intensity and the measurement of T_1 and T_2 relaxation times of the lung tissue. There is no doubt that if subsequently confirmed this would be of great clinical value.

The abdomen

The fetal liver is the most readily visible abdominal organ, which in part relates to its size and to its position below the high signal intensity of the fetal lungs. It possesses a homogeneous intermediate intensity signal. The portal and hepatic veins are also visible in most cases in the final trimester (Fig. 6).

The fetal kidneys were not visible with MRI. This may relate to their small size and lack of tissue contrast due to the paucity of retroperitoneal fat. Urine in the fetal bladder has a low signal intensity with a short TR and TE and depending on the volume in the fetal bladder is well seen (Fig. 7).

The musculoskeletal system

The musculoskeletal detail that could be obtained in the final trimester is more obviously dependent on the degree of movement occurring during the scan. Therefore the quality is variable. Of particular interest in the final trimester is the demonstration with T_1 weighted sequences of the layer of fetal subcutaneous fat. This possesses a high signal intensity due to its short T_1 relaxation time (Fig. 8), and is most prominent when imaging the buccal fat pad. Ultrasound assessment of poor fetal growth can be inaccurate, with a tendency to over-diagnosis (Deter *et al.* 1982), and measurement of the subcutaneous fat layer by MRI may be of value in the assessment of the growth-retarded infant (Stark *et al.* 1985). In our experience the quantitative measurement of the fat layer is difficult although a reasonable qualitative assessment may be possible. Further work is required to determine the usefulness of these observations.

The cardiovascular system

A central low intensity area representing the fetal heart may be seen with MRI from early in the second trimester. By the final trimester the cardiac image may be resolved into chambers (Fig. 9), but in our experience this is an unreliable finding. The image plane obtained through the heart is fortuitous and dependent on the fetal lie, so that interpretation may be difficult. Excel-

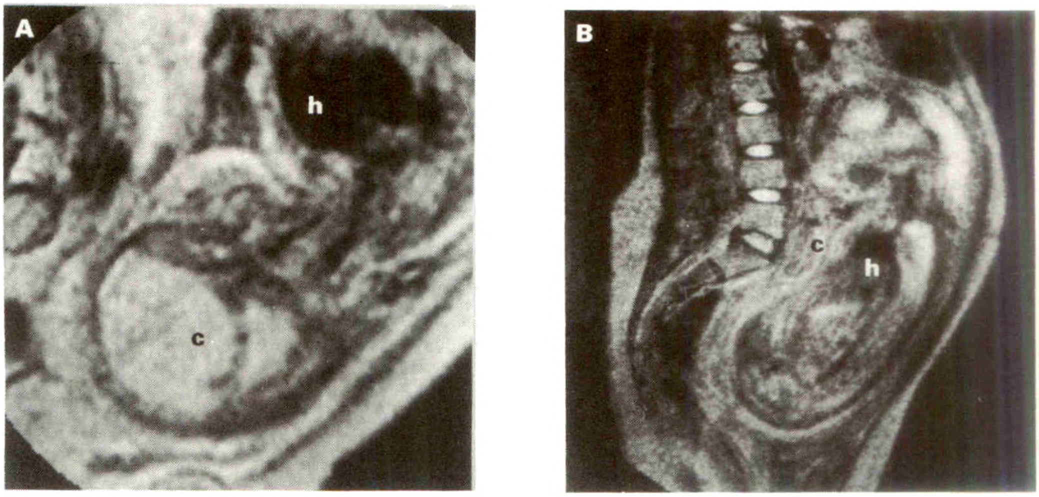

Fig. 10. Major vessels of (A) head and neck; (B) abdomen, heart (h), cerebral cortex (c), TR 2000 ms, T_2 80 ms.

lent images of the heart are readily available with ultrasound from early gestation and are capable of diagnosing most abnormalities that may occur (Allan 1983). The major vessels of the fetus are also seen as low intensity areas on T_2 weighted sequences (Fig. 10) and provide a unique view of their course in the chest and abdomen of the fetus. The low intensity of these images relates to the effect of blood flow on the MRI signal and is dependent on the rate of flow, turbulence and the image slice selected (Bradley & Waluch 1985). The nature of this phenomenon has led to studies on the measurement of rates of flow through vessels by MRI (Singer & Crooks 1983). This may have an application in obstetrics in the assessment of placental blood flow or the measurement of flow through the umbilical vessels. The umbilical vessels and the insertion into the placenta are well demonstrated with MRI (Fig. 11). The amniotic fluid

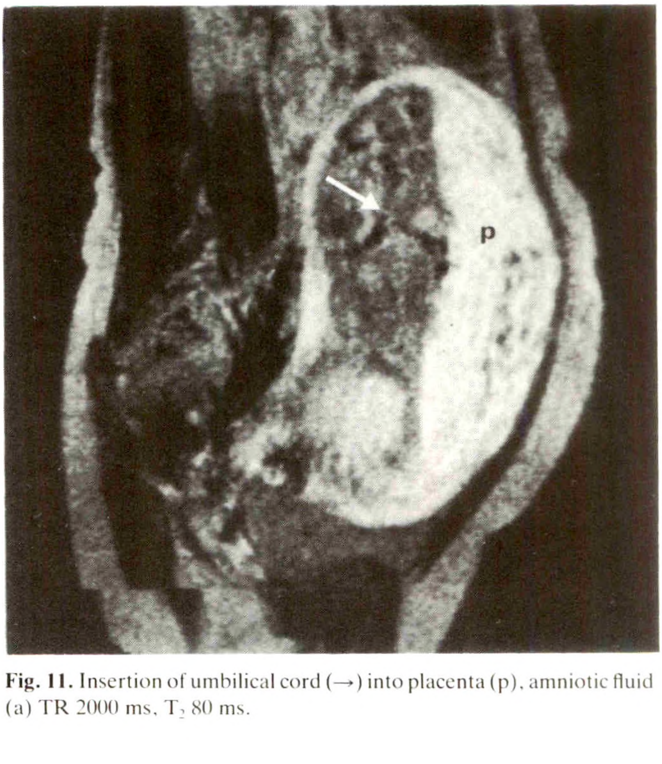

Fig. 11. Insertion of umbilical cord (→) into placenta (p), amniotic fluid (a) TR 2000 ms, T_2 80 ms.

behaves in a similar manner to urine having on both T_1 and T_2 pulse sequences used in this study a low signal intensity indicative of long relaxation times.

Discussion

Although MRI is a recently introduced imaging technique, it has made rapid progress to rival or surpass currently available imaging techniques. For the fetus, MRI has a drawback in not being a real time technique, so that fetal movement leads to a significant degradation of image quality. Nevertheless, in the final trimester of pregnancy, MRI can provide a unique display of fetal anatomy. We believe the role of MRI for the fetus will be only where ultrasound examination provides limited or unsatisfactory information.

A real time, so-called echoplanar technique, is under assessment, and has demonstrated its usefulness in the infant with cardiac abnormalities (Rzedzian *et al.* 1983). This may well overcome some of the problems with fetal movement that occur with the present MR systems.

References

Allan, L D. (1983) Early detection of congenital heart disease in prenatal life. *Clin Obstet Gynaecol* **10,** 507-514

Bradley, W. G & Waluch, V (1985) Blood flow. magnetic resonance imaging. *Radiology* **154,** 443-450

Bydder, G. M., Steiner, R. E & Young, I. R (1982) Clinical NMR imaging of the brain: 140 cases *AJR* **139,** 215-236

Cayea, P. D., Grant, D C., Doublet, P M. & Jones, T. B. (1985) Prediction of foetal lung maturity. inaccuracy of study using conventional ultrasound instruments. *Radiology* **155,** 473-475.

Deter, R. L , Hadlock, F. P & Harris, T. R B. (1982) Evaluation of normal foetal growth and the detection of intrauterine growth retardation In *Ultrasonography in Obstetrical Gynaecology* (Callen, P. W , ed), W B Saunders, Philadelphia, pp. 113-140.

Dobbings, J. & Sands, J (1973) Quantitative growth and development of the human brain *Arch Dis Child* **48,** 757-767.

Hadlock, F P., Irwin, J. F , Roecker, E , Shah, Y. P., Deter, R. L & Rossavik, I. K. (1985) Ultrasound prediction of fetal lung maturity. *Radiology* **155,** 469-472.

Hallman, M. & Teramo, K (1981) Measurement of the lecithin/spingomyelin ratio and phosphatidylglycerol in amniotic fluid: an accurate method of the assessment of fetal lung maturity. *Br J Obstet Gynaecol* **88,** 806-813.

Hawkes, R C., Holland, G N., Moore, W. S. & Worthington, B S. (1980) Nuclear magnetic resonance (NMR) tomography of the brain: a preliminary clinical assessment with demonstration A pathology. *J Comput Assist Tomogr* **4,** 577-582

Johnson, M. A., Pennock, J. M , Bydder, G. M. *et al* (1983) Clinical NMR imaging of the brain in children: normal and neurologic disease *AJR* **141,** 1005-1018.

Johnson, I. R., Symonds, E M., Kean, D., Worthington, B. S., Broughton Pipkin, F., Hawkes, R & Gyngell, M (1984) Imaging the pregnant human uterus with nuclear magnetic resonance. *Am J Obstet Gynecol* **148,** 1136-1139.

Larroche, J C. (1977) *Developmental Pathology of the Neonate.* Excerpta Medica, Amsterdam, pp. 269-276, 283-294, 319-444.

National Radiological Protection Board (1983) Revised guidance on acceptable limits of exposure during nuclear magnetic resonance clinical imaging. Br J Radiol **56,** 974-977.

Possmayer, F. (1982) The perinatal lung. In *The Biochemical Development of the Foetus and Neonate* (Jones, C., ed), Elsevier Biomedical Press, Amsterdam, pp 287-238

Rzedzian, R., Mansfield, P. & Doyle, M (1983) Real-time NMR clinical imaging in paediatrics. *Lancet* **ii,** 1281-1282

Singer, J. R & Crooks, L E. (1983) Nuclear magnetic resonance blood flow measurements in the human brain. *Science* **221,** 654-656.

Smith, F. W , Kent, C , Abramovich, D R. & Sutherland, H W (1985) Nuclear magnetic resonance imaging—a new look at the fetus. *Br J Obstet Gynaecol* **92,** 1024-1033

Stark, D. D , McCarthy, S M., Filly, R. A , Callen, P. W , Hricak, H. & Parer, J T (1985) Intrauterine growth retardation: evaluation by magnetic resonance. *Radiology* **155,** 425-427.

Steiner, R. E (1984) Nuclear magnetic resonance imaging of the heart and mediastinum. In *Nuclear Magnetic Resonance and its Clinical Applications* (Steiner, R E. & Radda, G. K., eds), British Medical Bulletin **40,** 191-193

Thieme, G A., Benjavic, R. A & Johnson, M. L (1983) Sonographic identification of lung maturation in the fetal lamb *Invest Radiol* **18,** 18-26

Yakolev, P I. & Lecours, A. R (1967) The myelogenetic cycles of regional maturation in the brain In *Regional Development of the Brain in Early Life* (Minkowski, A , ed), Blackwell Scientific Publications, Oxford, pp 3-69.

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Pathological prognostic indicators in cervical cancer with particular reference to patients under the age of 40 years

C. H. BUCKLEY, C. S. BEARDS, H. FOX

Summary. The presence of lymph node metastases in patients with cervical cancer is an important predictor of death and recurrence of disease. Lymph node metastases are more common in patients with mucus-secreting carcinomas than in women with pure squamous carcinomas even in what appears, clinically, to be early stage disease: such neoplasms are more frequent in women under the age of 40 years. The recognition of mucus secretion in a carcinoma and the detection of vascular permeation adjacent to the primary neoplasm identifies the patient at greatest risk of having pelvic lymph node metastases.

Whereas the number of women over the age of 40 years who die of cervical carcinoma in England and Wales has declined over the last 20 years, the number of women under the age of 40 who die of cervical cancer is increasing (Yule 1978; Hall & Monaghan 1983; Cook & Draper 1984). Many of these younger women present at a time when they appear, clinically, to have early stage disease, yet are subsequently shown to have widely disseminated microscopic metastases, thus the results of treatment are poor in these patients (Averette *et al.* 1975; Beecham *et al.* 1978; Piver *et al.* 1981; Matsuyama *et al.* 1984; Ward *et al.* 1985). It has been suggested that the neoplasms occurring in these younger women differ biologically and perhaps also histologically from the tumours that develop in older women (Wentz & Reagan 1959; Chung *et al.* 1981). Between 1979 and 1985 inclusive, a total of 246 cervical neoplasms were diagnosed and/or treated at St Mary's Hospital, Manchester. A histopathological examination of these tumours forms the basis of this report.

Materials and methods

All the material used was held on file in the Department of Pathology as blocks of paraffin-processed tissue and ranged from small, sometimes superficial or necrotic wedge biopsies of the cervix taken before radiotherapy, to extended hysterectomies with full pelvic node dissection. Routine haematoxylin and eosin stained sections were re-examined and those blocks which were regarded as the most representative were recut to provide sections for mucin and glycogen stains.

Tumours had been classified initially, in the first 5 years of the study, almost entirely on the basis of their general morphology, but reappraisal of the earlier cases (Beards 1983) led us, in 1983, to introduce routine mucin and glycogen stains and to reassign, where necessary, tumours diagnosed before this date (Tables 1 & 2). Tumours are now routinely stained with a combined PAS/alcian blue stain before and after treatment of the sections with diastase, the alcian blue being used at a pH of 2·4. This allows for the demonstration of both glycogen and a wide range of epithelial mucins.

Note was taken of the type and differentiation

Departments of Pathology, University of Manchester and St Mary's Hospital, Manchester
C. H. BUCKLEY
C. S. BEARDS
H. FOX

Correspondence: Dr C. H. Buckley, Department of Pathology, University of Manchester, Manchester M13 9PL

Table 1. Original histopathological diagnoses of 246 cervical carcinomas before the introduction of routine mucin stains

Original diagnoses	Number of women *n* (%)
Squamous carcinoma	187 (76)
Adenocarcinoma	28 (11·4)
Adenosquamous carcinoma	15 (6·1)
Undifferentiated carcinoma	10 (4·1)
Miscellaneous tumours	3 (1·2)
Metastatic tumours	3 (1·2)*
Total	246

* These three tumours are not included in the subsequent analysis.

of the tumours, the presence of vascular space permeation by carcinoma adjacent to the primary neoplasm, the presence of nodal metastases and such associated phenomena as cervical intraepithelial neoplasia (CIN), adenocarcinoma *in situ* (AIS) and features associated with human papillomavirus infection. A comparison was made between the pathological features of those carcinomas detected in women aged 39 years and under and those developing in older women.

Criteria for the diagnosis of squamous carcinoma

A diagnosis of well differentiated, keratinizing squamous carcinoma was made only when there were intercellular bridges and the formation of epithelial pearls: intracellular glycogen was a feature of some of these tumours. In the focally keratinizing, large-cell (moderately well differentiated) carcinomas there was a greater degree of cellular pleomorphism, intercellular bridges were absent or ill-defined and cell borders often indistinct: individually keratinized cells, identifiable by their eosinophilic cytoplasm, were present and sometimes were aggregated in the centres of cell groups but epithelial pearls were absent or very infrequent and poorly formed. In the absence of obvious cellular keratinization (poorly differentiated squamous carcinoma), the diagnosis depended for the most part upon the pattern of tumour growth, and the finding of rare dyskeratotic cells. This type of tumour was composed either of large cells resembling those of the keratinizing carcinomas and sometimes containing glycogen, or small cells, and had it not been for the occasional more differentiated focus, a diagnosis of undifferentiated tumour would have been inevitable. In nine tumours the range of differentiation was unusally wide, there being both well differentiated keratinizing areas and large- or small-cell non-keratinizing areas. In view of the fact that the two components were virtually equal in quantity, it was felt appropriate to designate these as squamous carcinomas with a wide range of differentiation.

Criteria for the diagnosis of adenocarcinoma

The majority of adenocarcinomas were well differentiated or moderately well differentiated and of typical endocervical type, being composed of branching glandular acini lined by mucin-secreting columnar cells: in the majority of these, mucus staining was copious and widespread, being present in both the cytoplasm and tumour acini. Other, moderately well differentiated neoplasms were also morphologically

Table 2. Revised histopathological diagnoses of 243 cervical carcinomas, frequency distribution by age of patients

	Age of patients (years)		
Type of tumour	≤39 *n* (%)	≥40 *n* (%)	Total *n* (%)
Squamous carcinoma	61 (55)	93 (70·5)	154 (63·4)
Adenocarcinoma	17 (15·3)	13 (9·8)	30 (12·3)
Adenosquamous carcinoma	15 (13·6)	10 (7·6)	25 (10·3)
Squamous carcinoma with mucin secretion	12 (10·8)	7 (5·3)	19 (7·8)
Undifferentiated	6 (5·4)	6 (4·5)	12 (4·9)
Other tumours	0 (—)	3 (2·3)	3 (1·2)
Total	111 (100)	132 (100)	243 (100)

adenocarcinomas being characterized by the presence of acini or tubular structures but mucus secretion was relatively scanty. A diagnosis of poorly differentiated adenocarcinoma was made when mucus secretion was widespread, though not necessarily uniform, and was present in intracellular and extracellular sites in at least 75% of the tumour. In some of these poorly differentiated carcinomas there was little or no glandular morphological differentiation.

Criteria for the diagnosis of adenosquamous carcinoma

A diagnosis of adenosquamous carcinoma, sometimes termed mucoepidermoid carcinoma, was made only when the neoplasm contained squamous and adenocarcinomatous elements and the minor component comprised at least one third of the total. The well differentiated adenosquamous carcinoma was recognized by the presence of well differentiated glandular elements (in this series only of endocervical pattern) and keratinizing squamous carcinoma. The rather less well differentiated carcinomas were morphologically less distinct but there was a squamoid pattern of growth together with mucus secretion in up to 50% of the tumour volume. The underlying squamous pattern was most commonly that of a large-celled non-keratinizing or focally keratinizing squamous carcinoma and the mucus-secreting areas of the tumour lay either in the middle of tumour islands or in the centres of trabeculae (Figs 1 & 2). Mucus-containing cells were of non-specific appearance or signet ring-like. Tumours containing areas resembling 'glassy cell' tumour were also included in this category, the distinguishing features being solid sheets or large, well-circumscribed islands of tumour cells with sharply defined cell borders, large vesicular nuclei with prominent nucleoli, copious clear or faintly eosinophilic cytoplasm and a trace of intracytoplasmic glycogen.

Criteria for the diagnosis of squamous carcinoma with mucus secretion

Some of the squamous carcinomas formed a distinct group which was characterized by the production of smaller quantities of mucus than were present in the adenosquamous carcinomas. The majority had the general morphology of non-keratinizing or focally keratinizing squamous carcinoma and mucus secretion was present in no more than 30% of the tumour volume. In most of them mucus was limited to the infiltrating and intravascular component of the neoplasm and less commonly to the centres of cell nests (Figs 3 & 4).

Criteria for the diagnosis of undifferentiated tumours

Tumours in which neither squamous nor adenocarcinomatous features could be identified, despite electron-optic studies in some, and in which attempts to identify endocrine cells, melanin and lymphoid characteristics had failed, were designated as undifferentiated.

Results

After the reappraisal, in particular the examination of mucin stains, modifications to the original classification proved necessary (Table 2).

Of the original group of 187 squamous carcinomas only 152 fulfilled the diagnostic criteria for squamous carcinoma after the application of mucin stains to the tumours classified before 1983 and the characterization of the group of squamous tumours with mucus secretion. In addition, two tumours regarded previously as undifferentiated were shown, on deeper sectioning, to be squamous carcinomas. In three of the tumours bizarre, pleomorphic tumour cells were present. Two were large-cell, focally keratinizing carcinomas and the other a non-keratinizing large cell neoplasm. The differentiation and age distribution of the squamous carcinomas is shown in Table 3. It is notable that 18·3% of the tumours in the older women were well differentiated, compared with only 6·6% of those in the younger women and that whilst the proportions of large-cell focally keratinizing carcinomas and large-cell non-keratinizing carcinomas were the same in the two groups, small-cell non-keratinizing carcinomas were more common in the younger women.

Of the 35 neoplasms no longer regarded as squamous carcinomas, 10 were reclassified as adenosquamous carcinomas, 18 as squamous carcinomas with mucus secretion and four were termed 'undifferentiated'. The most surprising change was that of three squamous carcinomas to adenocarcinomas; these tumours were diagnosed early in the study when a diagnosis of

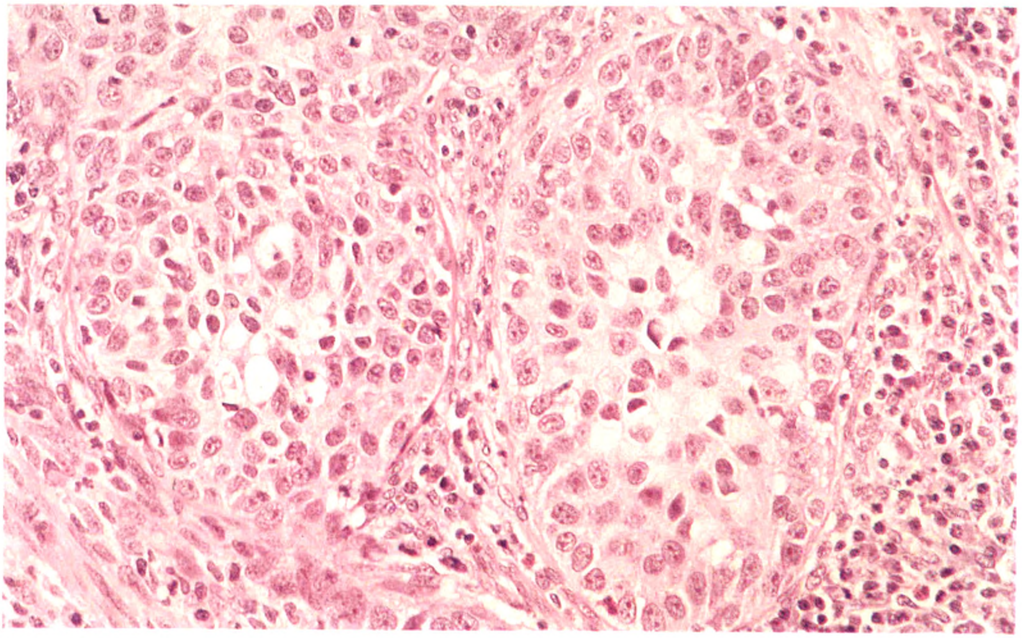

Fig. 1. A large-cell non-keratinizing invasive carcinoma with a lobular pattern. Haematoxylin and eosin.

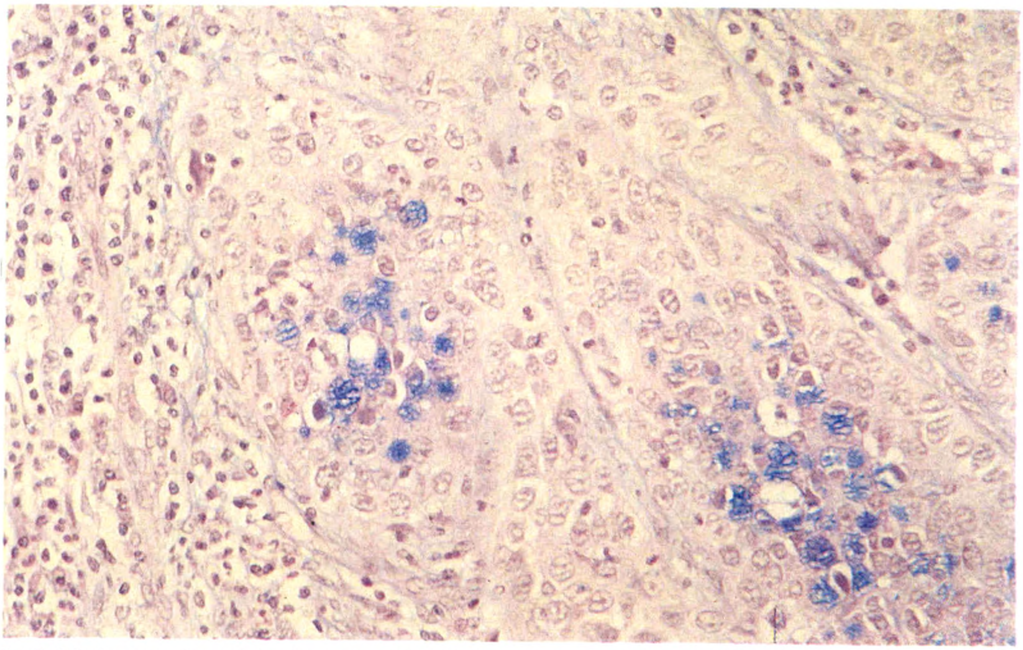

Fig. 2. Mucin-secreting cells in the centres of the lobules of the carcinoma shown in Fig. 1. PAS, alcian blue.

squamous carcinoma had been based upon the presence of large cells with copious eosinophilic cytoplasm which had been interpreted as keratinization. Re-examination demonstrated widespread, almost universal, intracellular mucus.

The group of 28 adenocarcinomas required less modification as they were, on the whole, far better differentiated and their diagnostic features subject to less misinterpretation. However, one was reclassified as an adenosquamous carcinoma and the final group of 30 adenocarcinomas included three 'squamous carcinomas'

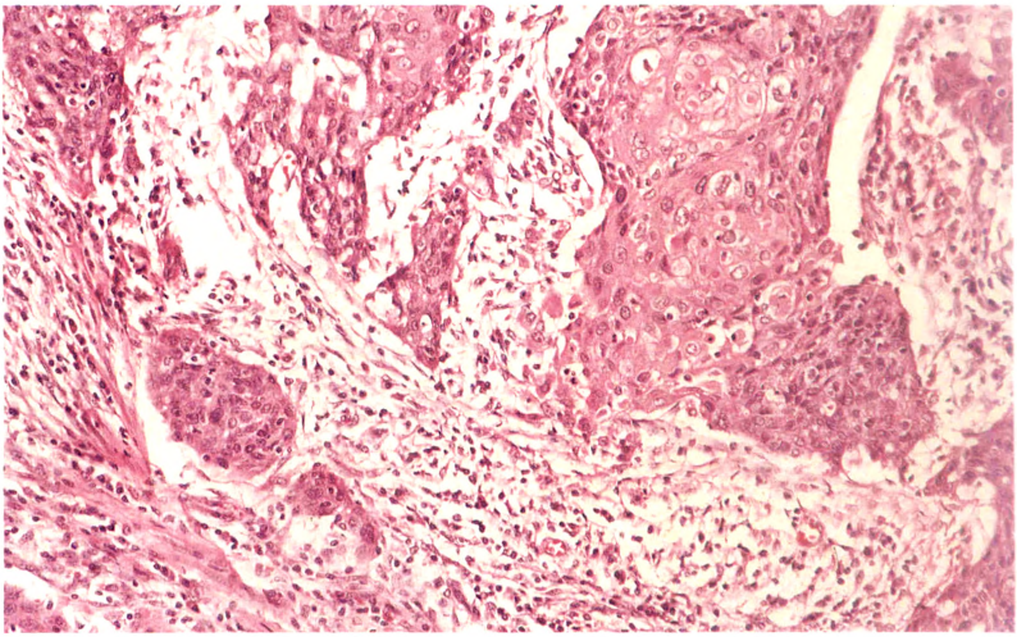

Fig. 3. A large-cell non-keratinizing, invasive squamous carcinoma. Haematoxylin and eosin.

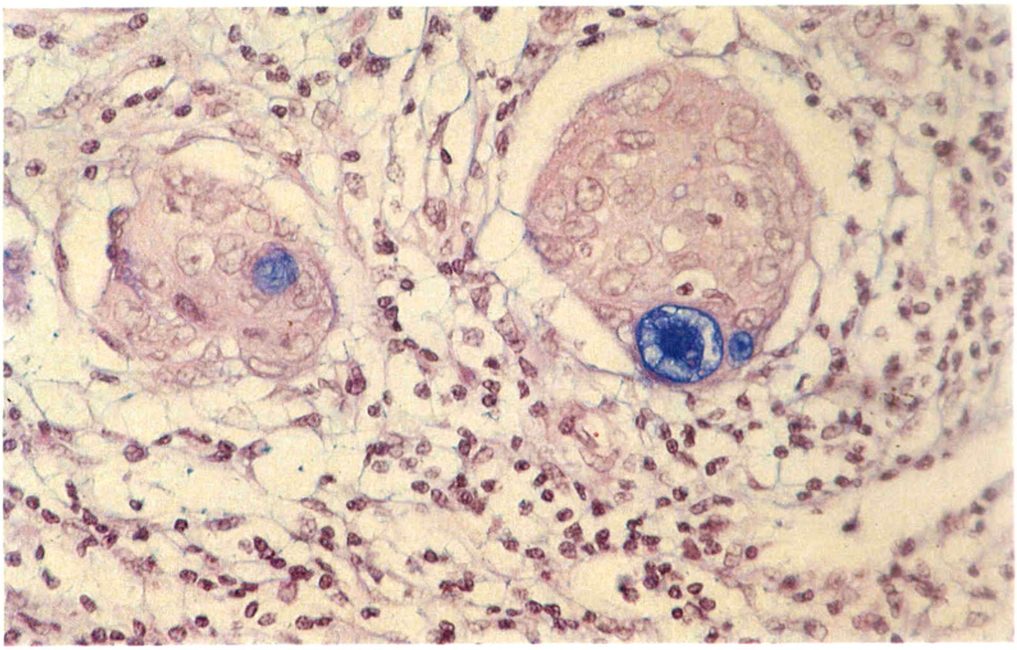

Fig. 4. Mucin-secreting cells (blue staining) at the infiltrating margin of the carcinoma shown in Fig. 3. PAS, alcian blue.

which had been later recognized as poorly differentiated adenocarcinomas.

Fifteen tumours were originally diagnosed as adenosquamous carcinomas. One of the original 15 was reassigned to the category of squamous carcinoma with mucus secretion and the diagnosis in the other 14 was confirmed. Ten neoplasms initially diagnosed as squamous carcinomas of moderate or poor differentiation and an adenocarcinoma were reclassified as adenosquamous carcinomas after mucin stains, a total of 25 adenosquamous carcinomas.

Table 3. Distribution of 154 squamous carcinomas by tumour differentiation and age of patients

Tumour differentiation	Age of patients (years) ≤39 *n* (%)	 ≥40 *n* (%)	 Total *n* (%)
Well differentiated, keratinizing	4 (6·6)	17 (18·3)	21 (13·6)
Large-cell, focally keratinizing	33 (54·1)	44 (47·1)	77 (50)
Large-cell, non-keratinizing	12 (19·7)	20 (21·5)	32 (20·8)
Small-cell, non-keratinizing	8 (13·1)	4 (4·3)	12 (7·8)
Small-cell, focally keratinizing	1 (1·6)	1 (1·1)	2 (1·3)
Wide range of differentiation	3 (4·9)	6 (6·5)	9 (5·8)
Unclassified	0	1 (1·1)	1 (0·6)
Total	61 (100)	93 (100)	154 (100)

Of the 19 tumours subsequently designated as squamous carcinoma with mucus secretion, 18 were originally thought to be unremarkable large-cell non-keratinizing squamous carcinomas and one had been termed a mucoepidermoid (adenosquamous) carcinoma but was considered, on reflection, to contain too small a proportion of mucin-secreting areas to warrant this diagnosis and was therefore reclassified.

Originally there were 10 tumours in which a classification proved impossible. This opinion was confirmed in eight of them but two were considered to possess sufficient squamous features on the recuts to demand reclassification as a large-cell focally keratinizing squamous carcinoma and a large-cell non-keratinizing carcinoma. Four of the carcinomas originally termed squamous were redesignated as undifferentiated tumours leaving 12 in this category.

The three tumours included in the miscellaneous group of 'other tumours' were two adenosarcomas and one mixed Mullerian tumour of high grade malignancy. All occurred in women ≥40 years of age.

The distribution of the neoplasms in the two age groups is shown in Table 2. More than half the total tumours (54·3%) occurred in women aged ≥40 years but certain types of carcinoma were more common in the younger women, 56·7% of adenocarcinomas, 60% of adenosquamous carcinomas and 63·2% of squamous carcinomas with mucus secretion occurred in women ≤39 years of age whereas more than half the squamous carcinomas (60·4%) presented in women aged ≥40 years; the undifferentiated neoplasms were evenly distributed between both age groups.

Treatment was not uniform in the two groups, women aged ≤39 years were more often treated by radical surgery (63·1%) compared with 19·4% of those aged ≥40 years (Table 4). This of necessity determined the material available for examination.

Lymph node metastases (Table 5) were present at the time of operation in 41 of the 95 patients (43·2%), 50% of those aged ≤39 years and 24% of those aged ≥40 years, despite the fact that with only two exceptions the patients were all thought, clinically, to be suitable for surgery, that is to have early stage disease.

In those patients having a squamous carcinoma, the overall risk of nodal metastases was 34·6% whereas it was only 16·7% in the older women. Of the patients with adenocarcinomas 42·9% had metastases, 45·5% of those ≤39 years of age and 33·3% of those aged ≥40 years.

In this series, well differentiated squamous carcinomas had metastasized in 3 of 9 cases (33·3%) and the corresponding numbers were 7 of 22 (31·8%) for focally keratinizing large-cell tumours; 4 of 13 (30·8%) for non-keratinizing large-cell tumours and 4 of 7 (57·1%) for small cell non-keratinizing tumours.

Adenosquamous carcinomas, squamous carcinomas with mucus secretion and undifferentiated tumours had metastasized most frequently, 53·8%, 66·7% and 50% respectively, whilst if the patients were ≤39 years of age, the corresponding percentages were 63·6%, 60% and 50% respectively.

In addition to the effect which the tumour histology appears to have had on the risk of nodal metastases, the presence of vascular per-

Table 4. The proportion of women treated by Wertheim's hysterectomy classified according to age and tumour pathology

	Patients treated by Wertheim's hysterectomy	
Type of tumour	≤39 years *n*/*n* (%)	≥40 years *n*/*n* (%)
Squamous carcinoma	34/61 (55·7)	18/93 (19 4)
Adenocarcinoma	11/17 (64·7)	3/13 (23 1)
Adenosquamous carcinoma	11/15 (73·3)	2/10 (20)
Squamous carcinoma with mucin secretion	10/12 (83·3)	2/7 (28 6)
Undifferentiated	4/6 (66·7)	0/6 (—)
Total	70/111 (63·1)	25/129 (19.4)

Table 5. Distribution of lymph node metastases in patients treated by Wertheim's hysterectomy by tumour pathology and age of patients

	The risk of metastases		
Type of tumour	Overall *n*/*n* (%)	≤39 years *n*/*n* (%)	≥40 years *n*/*n* (%)
Squamous carcinoma	18/52 (34·6)	15/34 (44·1)	3/18 (16 7)
Adenocarcinoma	6/14 (42·9)	5/11 (45·5)	1/3 (33 3)
Adenosquamous carcinoma	7/13 (53·8)	7/11 (63·6)	0/2 (—)
Squamous carcinoma with mucin secretion	8/12 (66·7)	6/10 (60)	2/2 (100)
Undifferentiated	2/4 (50)	2/4 (50)	0 (—)
All tumours	41/95 (43·2)	35/70 (50)	6/25 (24)

meation by tumour (Table 6) in the vicinity of the primary carcinoma increased the overall risk of nodal metastases from 12·5% to 49·4%. If the patient had a tumour of a type associated with a higher than average risk of metastases (adenosquamous carcinoma or squamous carcinoma with mucus secretion) and had, in addition, vascular permeation, the risk of the presence of nodal metastases in clinical stage I disease reached 60%. Of those patients aged ≤39 years in whom there was vascular infiltration, metastases had developed in 63·6% of adeno-

Table 6. Distribution of lymph node metastases in relation to vascular permeation by tumour pathology and age of patients

	Risk of metastases					
	Vascular permeation present			Vascular permeation absent		
Type of tumour	Overall *n*/*n* (%)	≤39 years *n*/*n* (%)	≥40 years *n*/*n* (%)	Overall *n*/*n* (%)	≤39 years *n*/*n* (%)	≥40 years *n*/*n* (%)
Squamous carcinoma	16/42 (38·1)	13/27 (48·1)	3/15 (20)	2/10 (20)	2/7 (28·6)	0/3 (—)
Adenocarcinoma	6/9 (66·7)	5/7 (71·4)	1/2 (50)	0/5 (—)	0/4 (—)	0/1 (—)
Adenosquamous carcinoma	7/13 (53·8)	7/11 (63·6)	0/2 (—)	0 (—)	0 (—)	0 (—)
Squamous carcinoma with mucin secretion	8/12 (66·7)	6/10 (60)	2/2 (100)	0 (—)	0 (—)	0 (—)
Undifferentiated	2/3 (66·7)	2/3 (66·7)	0 (—)	0/1 (—)	0/1 (—)	0 (—)
All tumours	39/79 (49·4)	33/58 (56·9)	6/21 (28·6)	2/16 (12·5)	2/12 (16·7)	0/4 (—)

squamous carcinomas, 60% of squamous carcinomas with mucus secretion, 66·7% of undifferentiated tumours and 48·1% of squamous carcinomas. The corresponding numbers for those patients in whom vascular permeation was not detected were nil for adenocarcinomas, adenosquamous carcinomas, squamous carcinomas with mucus secretion and undifferentiated carcinomas and 28·6% for squamous carcinomas. Unfortunately, in these categories the number of patients aged ≥40 years was too small to analyse but patients having squamous carcinomas had a 20% risk of developing metastases if there was vascular permeation, but none if vascular spaces were not infiltrated by tumour The presence of vascular space permeation by tumour altered the risk of nodal metastases in patients having an adenocarcinoma from 42·9% overall to 66·7% overall and if the patient was ≤39 years of age, the risk was 71% (5 of 7).

There were three tumours in which the manner of infiltration was unusual. This occurred directly through the basement membrane of the epithelium from which the tumour developed, straight into the adjacent vasculature. Only one patient, a 35-year-old woman, was treated by radical surgery and she had no pelvic nodal metastases.

Intraepithelial neoplasia adjacent to the tumour was found in 139 of the 197 tumours (70·6%) that had sufficient material for assessment (Table 7). The age of the patient did not significantly alter the frequency with which intraepithelial neoplasia was diagnosed.

Discussion

A classification of cervical tumours based only upon a morphological assessment suggests that more than 90% are squamous carcinomas; however, the application of more precise criteria for the recognition of these neoplasms, in particular the application of mucin stains (Benda *et al.* 1985), reveals that only 65–70% are actually squamous carcinomas, the others being mainly adenocarcinomas, adenosquamous carcinomas and squamous carcinomas with mucus secretion. The importance of recognizing these mucus-containing neoplasms has been clearly shown by Benda *et al.* (1985) and is confirmed by the present study. All mucus-secreting neoplasms exhibit an increased tendency to metastasize to the regional lymph nodes compared with squamous carcinomas even in what is thought clinically to be early stage disease and no cervical cancer should be classified without the application of mucin stains.

The presence of lymph node metastases at the time of primary surgery for cervical carcinoma is significant in predicting death from disease or recurrence (Benda *et al.* 1985). In the current series, 43·2% of patients had pelvic lymph node metastases at the time of surgery although clinically they were considered to be in stage IB (FIGO) or stage IIA. Metastases were frequently of extremely small size and detectable only by microscopic examination. They occurred from primary tumours of both small and large bulk, and the smallest tumour from

Table 7. Intraepithelial neoplasia associated with 197 specimens of invasive cervical carcinomas

Type of tumour	No. of specimens (*n* = 197)	No. with CIN	No. with AIS	Percentage with intraepithelial neoplasia	No with KA
Squamous carcinoma	123	97	8*	78·9	20
Adenocarcinoma	26	7	12†	50·0	2
Adenosquamous carcinoma	21	14	1‡	66·7	2
Squamous carcinoma with mucin secretion	18	13	1‡	72·2	4
Undifferentiated	9	2	0	22·2	0

* All eight patients also had CIN

† Six of 12 also had CIN.

‡ This patient also had CIN

Of the patients with squamous carcinoma, two had VAIN but no CIN, one had VIN and CIN, and one had AIS, CIN and KA Of the patients with adenosquamous carcinoma, one had microglandular hyperplasia and one had VIN. One patient with squamous carcinoma with mucin secretion had VIN

AIS, Adenocarcinoma *in situ;* CIN, cervical intraepithelial neoplasia, VIN, vulval intraepithelial neoplasia; VAIN, vaginal intraepithelial neoplasia, KA. koilocytotic atypia.

which extensive pelvic node metastases had developed measured only 4·5 mm in its greatest depth and would have been regarded by some observers, as a micro-invasive carcinoma although its greatest diameter was in fact 10 mm and its bulk exceeded 200 mm^3 which most workers now regard as the limit for inclusion in the micro-invasive category when vascular space permeation is present (Burghardt 1984).

In this series, women ≤39 years of age were at greater risk of having nodal metastases (50% compared with 24% in the patients ≥40 years of age). It is easy to conclude that the tumours in the younger woman must therefore be distinctive and differ in some way from those occurring in the older woman, and although to some extent this is correct, it is not the entire explanation

Adenosquamous carcinoma and squamous carcinoma with mucin secretion were certainly more common in the younger patients and both types of tumour were more likely to have metastasized than were squamous carcinomas or adenocarcinomas; the highest risk of metastatic disease being in the younger woman with an adenosquamous carcinoma or a squamous carcinoma with mucus secretion. However, the younger patients were also more likely to have metastases when they had an unremarkable squamous carcinoma or adenocarcinoma. Indeed, the greatest risk of metastases (71%) was observed in women ≤39 years who had an adenocarcinoma and in whom vascular space permeation was present adjacent to the primary neoplasm. Vascular space permeation must therefore also be regarded as an important prognostic factor because when this was present metastases occurred in almost 50% of cases whilst in the absence of permeation, only 12·5% had metastasized.

The management of a patient with cervical cancer is based upon the results both of the clinical examination and the cervical biopsy. It is important therefore that the pathologist identifies those patients, whatever their age, in whom there is a risk that metastases have already occurred. They are the patients in whom the cervical tumour is producing mucus and in whom there is vascular permeation adjacent to the primary neoplasm. Such patients can be expected to have lymph node metastases in the pelvis even when the clinical assessment suggests that the disease is in stage I or IIA. The affected lymph nodes are rarely enlarged, cannot be detected by screening techniques and, because of the random distribution and small size of the nodal metastases, fine needle aspiration of the pelvic nodes is not recommended

The cervical screening programme in the UK has concentrated on the women aged ≥35 years and in this group the number of patients dying from cervical cancer has diminished. It could be argued that this is the result of identifying patients when their disease is still at a pre-invasive stage and that there should, as a consequence, be a progressive decrease in the number of invasive neoplasms registered. This is, however, not supported by the registration data which clearly demonstrate an absolute increase in both pre-invasive and invasive cervical neoplasia (Cook & Draper 1984) in younger women in England and Wales and an increase in deaths from cervical cancer in women aged ≤35 years from 35 deaths in 1964 to 114 in 1985 (Parliamentary reply 1986). Not only has carcinoma become more common but the course of the disease in women aged <40 often differs from the traditional pattern. The identification of the women at greatest risk of having aggressive disease at an early stage of their management is therefore of increasing clinical importance.

References

Averette, H E , Ford, J H., Dudan, R. C , Girtanner, R E , Hoskins, W J. & Lutz, L H (1975) Staging of cervical cancer. *Clin Obstet Gynecol* **18**, 215-232

Beards, C S (1983) A study of histological and clinical features of carcinoma of the cervix and their relation to prognosis *BSc Thesis*. Victoria University of Manchester

Beecham, J. B , Halvorsen, T & Kolbenstvedt, A (1978) A histologic classification of lymph node metastases and patient survival in stage IB cervical cancer *Gynaecol Oncol* **6**, 95-105

Benda, J A , Platz, C E , Buchsbaum, H & Lifshitz, S. (1985) Mucin production in defining mixed carcinoma of the uterine cervix· a clinicopathologic study *Int J Gynecol Pathol* **4**, 314-327.

Burghardt, E (1984) Microinvasive carcinoma in gynaecological pathology. *Clin Obstet Gynaecol* **11**, 239-257.

Chung, C. P., Stryker, J. A., Ward, S. P , Nahhas, W A & Mortel, R (1981) Histologic grade and prognosis of cancer of the cervix *Obstet Gynecol* **57**, 636-641

Cook, G. A. & Draper, G J. (1984) Trends in cervical cancer and carcinoma *in situ* in Great Britain *Br J Cancer* **50**, 367-375

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An analysis of uterine activity in spontaneous labour using a microcomputer

F. M. FAIRLIE, G. F. PHILLIPS, B. J. ANDREWS, A. A. CALDER

Summary. A microcomputer was used to analyse uterine activity during spontaneous labour in 30 nulliparous and 30 parous patients. The intrauterine mean active pressure (MAP) in the nulliparous group was 1·51 kPa (SD 0·45) in the first stage and 2·71 kPa (SD 0·77) in the second stage. For the parous group, the MAP in the first stage was 1·22 kPa (SD 0·37) and in the second stage was 2·92 kPa (SD 0·98). A significant parity difference in MAP and contraction frequency was observed in the first stage but not in the second stage. Epidural analgesia did not appear to influence uterine activity in the first stage but was associated with a lower MAP, contraction frequency and intensity in the second stage. During the first stage, MAP increased by 21% in nulliparas and by 39% in multiparas. The rise in MAP was mainly due to an increase in contraction frequency.

If the management of labour is to be optimal, an appreciation of normal uterine activity and the factors which influence progress and fetal well-being is essential. Steer *et al.* (1984), Gibb *et al.* (1984) and Arulkumaran *et al.* (1984) recorded intrauterine pressure changes during spontaneous labour. Uterine activity was quantified on-line by using the Sonicaid Uterine Activity Integrator to measure the uterine activity integral (UAI) (Steer 1977). A disadvantage of this system is that quantification is restricted to intervals of 15 min and thus total activity cannot be distinguished from the level of activity. With the aim of improving on current methods of quantification, we have designed a microcomputer-based system capable of measuring and analysing intrapartum intrauterine pressure changes. Unlike the Sonicaid Uterine Activity Integrator, we can compute both total activity and the level of activity for time intervals of varying length and at any stage in labour. A further advantage of our system is the ability to derive values for the components of uterine activity, i.e. contraction frequency, intensity and duration. Although computers have been employed to analyse uterine activity for over a decade (Crawford 1975; Tromans *et al.* 1982), a system which independently calculates the three components of activity has not been reported previously.

There are many factors which could influence intrapartum uterine activity. We have confined our study to patients in spontaneous labour who progress normally and are delivered vaginally. Our intention was to test our equipment in a clinical setting, investigate the effect of parity, progress in labour and analgesia on uterine activity and compare the results obtained with those achieved by other investigators using less sophisticated methods of data collection and analysis. In the past, relatively little attention has been paid to the second stage of labour and we have therefore continued to record intrauterine pressure until delivery.

The Royal Maternity Hospital, Glasgow
F. M FAIRLIE *Research Registrar*

Bioengineering Unit, Strathclyde University, Glasgow
G. F. PHILLIPS *Research Assistant*
B. J. ANDREWS *Lecturer*

University Department of Obstetrics and Gynaecology, Edinburgh
A. A. CALDER *Professor*

Correspondence: Dr F. M. Fairlie

Patients and methods

Patients were recruited from admissions to the labour ward of Glasgow Royal Maternity Hospital. The study group comprised 30 nulliparous and 30 parous patients in spontaneous labour at term. All patients were white European and no limits were set for maternal age or height. The parous patients were of low parity (two or less) with no history of caesarean section. Spontaneous labour was defined as regular uterine contractions with the cervix no more than 1 cm long and dilated to at least 2 cm. Progress in labour was defined as normal if the rate of cervical dilatation exceeded 0·5 cm/h. Patients were excluded from the study if they had ruptured membranes, if oxytocin or prostaglandin was used to augment uterine activity or if delivery was by caesarean section.

The onset of the first stage was defined as the time when amniotomy was performed. This procedure was performed early in established labour in accordance with hospital policy (Stewart *et al.* 1982). Immediately after rupturing the membranes, a Gaeltec intrauterine catheter was introduced into the amniotic cavity using the technique described by Steer *et al.* (1978). A continuous record of the fetal heart rate (FHR) and the intrauterine pressure was provided by a Hewlett Packard 8030A monitor. In keeping with our hospital practice, vaginal examinations were made every 3–4 h unless otherwise indicated. Pain relief was obtained from either inhalation of the nitrous oxide/oxygen mixture ('Entonox'), intramuscular pethidine 100–150 mg or epidural analgesia. The mode of analgesia administered was determined primarily by patient choice.

Most patients decided to remain in bed throughout their labour adopting either a semi-recumbent or a lateral position. A few opted initially to sit in an armchair but soon returned to bed once contractions became painful. Four patients were delivered on a birthing chair. The intrauterine catheter was removed with delivery of the head and the immediate neonatal condition was recorded in terms of Apgar scores.

Analysis of uterine activity

The analysis of intrauterine pressure depends on the recognition of contractions and estimation of the baseline. We used a BBC B microcomputer programmed to recognize the start of a contraction as a sustained positive rise of pressure, provided that the mean pressure in the period 10–30 s after the start of the contraction exceeds the baseline by a pre-set threshold of 7·5 mmHg. The end of a contraction is recognized when the rate of change of pressure returns to zero after having achieved a requisite negative value. The measure of the rate of change of pressure is the median second–second difference in pressure over a 20-s period. This measure ensures that pressure changes are only taken into account if they are sustained over a period of time. Rapid changes, as when the patient coughs, are ignored. Baseline pressure is re-evaluated at every second between contractions. A recursive digital filter is modified to produce a smoothed pressure curve biased towards lower pressure values.

Quantification of uterine activity

The method of measuring the UAI (Steer 1977) is limited to consideration of 15-min time intervals. A system of units which avoids this restriction has been proposed by Phillips & Calder (1987) and is used in this study. The total activity of the uterus over any period of time is described by the active pressure integral (API), in units of kilopascal seconds (kPa s). This is defined as the sum, at 1-s intervals, of the intrauterine pressure minus the baseline pressure. The level of uterine activity during that time is found by dividing the API by the number of seconds over which the pressure is integrated. The mean value of the active pressure is thus obtained and is known as the mean active pressure (MAP) expressed in kPa. The MAP can be directly compared with the UAI after dividing the latter by 900 (the number of seconds in 15 min).

The level of activity (MAP) has three components, the mean frequency, intensity and duration of contractions. The mean contraction frequency (MCF) and the mean contraction duration (MCD) are self-explanatory. A measure of the intensity of contractions is obtained by dividing the API by the total duration of contractions. This results in the mean value of the active pressure recorded during contractions, which is known as the mean contraction active pressure (MCAP), expressed in kPa. Provided that SI units are used throughout, it can be shown that $\mathrm{MAP} = \mathrm{MCF} \times \mathrm{MCD} \times \mathrm{MCAP}$, and that the product of MCF (in Hz) and

MCD (in s) represents the proportion of time spent contracting.

Statistical methods

The recorded variables were all tested for normality with the Kolmogorov–Smirnov *Z*-test. All were found to follow a normal distribution except for the duration of the second stage. Mean values and the Student's *t*-test were used to test for statistical significance.

Results

Table 1 defines the maternal and neonatal characteristics of the patients studied. There was no significant difference between the nulliparous and the parous groups in terms of height, initial cervical dilatation, Bishop score and birthweight. Only two infants had Apgar scores of <7 at 5 min. No neonatal morbidity was encountered. Epidural analgesia was administered to 16 (53%) nulliparous patients and 4 (13%) parous patients. Thirteen patients required to be delivered by forceps. All were nulliparous. The indication for operative delivery was failure to progress in 10 and fetal distress in three women. Nine of the former group and one of the latter had been given epidural analgesia. All the instrumental deliveries were non-rotational.

Influence of parity on uterine activity

Table 2 compares the two parity groups. The API was significantly higher in the nulliparous group for both the first and the second stage Labour duration accounted for most of this difference since in the first stage, duration was

Table 1. Maternal and neonatal characteristics in nulliparous and parous patients

	Nulliparous (n = 30)		Parous (n = 30)	
Characteristic	Mean (SD)	Range	Mean (SD)	Range
Age (years)	23·7 (4·4)	17·0 –33·0	26·6 (4·3)	20·0 –37 0
Height (m)	1·61 (0·07)	1·49– 1·79	1 61 (0·51)	1 54– 1 73
Gestation (weeks)	39·8 (0·9)	37·5 –41 0	39 6 (1 1)	38·0 –41·0
Bishop score	9·2 (1·1)	8·0 –12 0	8·7 (1·4)	6 0 –11·0
Dilatation at catheter insertion (cm)	4·0 (1·1)	2·5 – 6·5	4·2 (1·1)	3·0 – 6·5
Birthweight (kg)	3·27 (0·43)	2·28– 4·04	3 42 (0·42)	2·45– 4·30
Apgar score				
at 1 min	7·9 (1·9)	1 0 –10·0	8·0 (1·9)	2·0–10·0
at 5 min	9·7 (0·6)	8·0 –10·0	9·4 (1·4)	3·0–10 0

Table 2. The influence of parity on uterine activity

	First stage		Second stage	
Uterine activity	Nulliparous Mean (SD)	Parous Mean (SD)	Nulliparous Mean (SD)	Parous Mean (SD)
Duration (min)	*233 (106)	143 (85)	*88 (57)	27 (37)
API (kPa s)	*20 950 (13 100)	10 420 (6 440)	*12 610 (6770)	4050 (4120)
MAP (kPa)	*1·51 (0·45)	1 22 (0·37)	2·71 (0·77)	2 92 (0·98)
MCAP (kPa)	2·24 (0·46)	2·06 (0·46)	3·44 (0·81)	3·73 (1·20)
MCF (*n*/10 min)	*3 89 (0·77)	3·47 (0·75)	5·01 (0·79)	5·07 (1·00)
MCD (s)	103·5 (8·41)	103 4 (10·83)	94·5 (8·4)	94·9 (15·2)
Time spent contracting (%)	*66 0 (11·0)	59·0 (9·0)	76·0 (8·0)	76·0 (11 0)

Significance of difference between the two parity groups for the same stage of labour

* $P<0·05 >0·01$ (*t*-test, two tailed)

There were no second stage data for two parous patients as the catheter became dislodged at full dilatation greater in the nulliparous group by a factor of 1·63 while MAP was greater by a factor of only 1·24 and in the second stage, duration was greater in the nulliparous group by a factor of 3·24 whereas the difference in MAP did not reach statistical significance.

The MAP in the first stage was significantly higher for nulliparous patients. This was due to a greater contraction frequency since there was no parity difference with respect to contraction amplitude or duration. In the first stage, the time spent by the uterus in a contractile state was significantly greater for nulliparous patients There was no such parity difference in the second stage.

The higher level of first stage uterine activity in the nulliparous patients compared with the parous patients and the absence of any such difference in the second stage is a true parity effect since it was still present when nulliparous patients receiving pethidine or Entonox were compared with multiparous patients receiving pethidine or Entonox (Table 3).

Analgesia and uterine activity

Nulliparous patients receiving epidural analgesia were compared with nulliparous patients receiving pethidine or Entonox (Table 4). The difference between the two groups in cervical dilatation at catheter insertion was not significant. Epidural analgesia was associated with a significantly longer duration and greater API in both the first and the second stage of labour. In the first stage of labour, there was no difference in the MAP or its components between patients given an epidural and those given pethidine or Entonox. In the second stage, the MAP, contraction frequency and MCAP were all significantly lower in association with epidural analgesia. A similar analysis could not be per-

Table 3. The influence of parity on uterine activity in patients receiving pethidine or Entonox

	First stage		Second stage	
	Nulliparous ($n = 14$) Mean (SD)	Parous ($n = 26$) Mean (SD)	Nulliparous ($n = 14$) Mean (SD)	Parous ($n = 26$) Mean (SD)
API (kPa s)	*14 700 (7000)	93 000 (5400)	*9991 (6610)	3095 (1505)
MAP (kPa)	*1·56 (0·47)	1·22 (0·39)	3·15 (0·68)	2·91 (1·21)
MCAP (kPa)	2·29 (0·57)	2·07 (0·49)	3·88 (0·78)	3·70 (1·50)
MCF (*n*/10 min)	*4·0 (0·73)	3·43 (0·77)	5·33 (0·80)	4·95 (1·55)
MDC (s)	103 (10)	103 (11)	92·3 (9·10)	89·9 (24·0)

* $P<0{\cdot}05 >0{\cdot}01$ (*t*-test, two-tailed) comparing the nulliparous with the parous groups for the same stage of labour

Table 4. A comparison of nulliparous patients receiving epidural analgesia with nulliparous patients receiving pethidine/Entonox

	First stage		Second stage	
	Epidural ($n = 16$) Mean (SD)	Pethidine/Entonox ($n = 14$) Mean (SD)	Epidural ($n = 16$) Mean (SD)	Pethidine/Entonox ($n = 14$) Mean (SD)
Cervical dilatation (cm)	3·7 (1·0)	4·3 (1·1)		
Duration (min)	**292 (89)	165 (82)	**116·5 (57·5)	55·3 (37·0)
API (kPa)	*26 400 (14 700)	14 700 (7400)	*14 900 (6200)	10 000 (6600)
MAP (kPa)	1·46 (0·45)	1·56 (0·47)	**2·32 (0·64)	3·15 (0·68)
MCF (*n*/10 min)	3·78 (0·82)	4 01 (0·73)	*4·72 (0·67)	5·34 (0·80)
MCAP (kPa)	2·19 (0·36)	2·29 (0·57)	**3·05 (0·62)	3·88 (0·78)
MCD (s)	104·0 (7·0)	103·0 (10·0)	96·3 (7·5)	92·0 (9·0)

* $P<0{\cdot}05 >0{\cdot}01$.
** $P<0{\cdot}01$.

formed for the parous group since only four epidurals were given.

In Table 5, the level of uterine activity for the 20 min before epidural administration was compared with the 20 min after epidural administration. There was no significant difference in MAP or in any of its three components.

The trend in uterine activity as labour progresses

The first stage was divided into three equal time periods. The MAP and its components were calculated for each period (Table 6). A group of patients starting at a comparable stage of labour was selected by excluding those with a cervical dilatation >4 cm at the time of intrauterine catheter insertion. Patients were grouped according to parity. Comparing mean values for the first and the last time period, MAP rose by 21% in nulliparas and by 39% in multiparas. In both parity groups, this rise was mainly due to more frequent contractions, although in the parous group there was also a significant rise in MCAP. The MAP for the first 15 min after amniotomy and intrauterine catheter insertion was compared with the MAP for the second 15-min interval. No significant difference was found (Table 7). Furthermore there was no difference between the MAP in the first 15 min after catheter insertion and the whole of the first third of the first stage.

A comparison was made between the first and second stages of labour. Two multiparous patients were excluded because the intrauterine pressure catheter became dislodged before delivery. The remaining 58 patients all showed a significantly higher MAP, MCAP and MCF in the second stage compared with the first stage ($P<0·001$ paired t-test.) There was no difference in the MCD. The rise in MCF was greater than the rise in MCAP and accounted for most of the increase in MAP. The percentage of each stage of labour occupied by uterine contractions (time spent contracting) was compared and found to

Table 5. The short-term effect of epidural analgesia on the mean active pressure (MAP)

	Mean active pressure (kPa)	
	Before epidural	After epidural
Nulliparous	1·55	1·76
(n = 15)	1·59	1·26
	1·98	2·68
	1·09	1·78
	1·20	0·44
	1·97	1·70
	0·98	0 98
	2·39	2·06
	1 36	1·86
	1·28	1·52
	0·64	0·79
	0·81	0·64
	1·98	1·63
	1·57	1·37
	1·89	1·70
Parous	1·68	1·38
(n = 4)	1·46	1 62
	1·25	1·40
	1·13	1 17
Mean	1·46 (SD 0·45)	1·46 (SD 0·52)

One nulliparous patient was excluded as epidural was administered before insertion of the intrauterine pressure catheter.
Comparing pre- and post-epidural MAP $P>0·05$ paired t-test

Table 6. Analysis of the first stage of labour by thirds, comparing nulliparous with parous groups and excluding those with a cervical dilatation greater than 4 cm

Uterine activity	Nulliparous (n = 22) Mean (SD)	Parous (n = 18) Mean (SD)
MAP (kPa)		
First	1·38 (0·54)	1·03 (0·39)
Second	1·58 (0·53)	1·18 (0·37)
Third	*1·67 (0 49)	*1·43 (0·38)
Frequency (n/10 min)		
First	3·80 (0·99)	3·20 (0 97)
Second	4·00 (0·78)	3·39 (0·93)
Third	*4·34 (0·98)	*3·88 (0·87)
MCAP (kPa)		
First	2·09 (0·50)	1·94 (0·48)
Second	2·28 (0·46)	2·02 (0·48)
Third	2·25 (0·40)	*2·20 (0·50)
MCD (s)		
First	102·7 (9·2)	101·0 (12·2)
Second	102·3 (5·9)	105·0 (10·0)
Third	102·5 (10·9)	102·6 (12·8)

Significance of difference comparing the first third with the last third time period, paired t-test for individual patients within each parity group *$P<0·05$ $>0·01$.

Table 7. A comparison of the MAP during the first and second 15-min periods after amniotomy and intrauterine catheter insertion for individual patients within each parity group

	Nulliparous (n = 14) Mean (SD)	Parous (n = 26) Mean (SD)
First 15 min	1·16 (0·54)	1·04 (0·50)
Second 15 min	1·30 (0·60)	1·07 (0·49)

Paired t-test $P>0·05$ for individual patients within each parity group

be significantly greater in the second stage ($P<0·001$ paired t-test.)

Figures 1a and 1b compare uterine activity in the last 15 min of the first stage with the first 15 min of the second stage. The 31 patients who pushed before the diagnosis of full dilatation were excluded. A significant rise ($P<0·001$) in the MAP occurred only if the first 15 min of the second stage were associated with pushing efforts (Fig. 1b).

Discussion

Although the application of a computer to analyse intrapartum uterine activity is not a new concept, a system capable of both measuring the active contraction area and deriving three components of the total myometrial activity has not been described before or used in a clinical setting. We recognize that our definitions of normal progress and the onset of the first stage are artificial. Some degree of inaccuracy also exists in identifying the beginning of the second stage. These practical problems are common to all studies of spontaneous labour and should be kept in mind when interpreting observations.

The time spent contracting was surprisingly high. The microcomputer assumes that a contraction begins when the intrauterine pressure first starts to rise and ends only when the pressure curve has completely levelled out again.

This may result in an overestimate of the duration of contractions Alternative methods based on threshold pressures tend to underestimate contraction duration and thus values presented by different authors cannot be directly compared. In keeping with other studies, however, we found no change in the mean contraction duration as labour progressed.

We would agree with the comment made by Gibb *et al.* (1984) that a wide range of uterine activity is compatible with normal progress in spontaneous labour. Our values for MAP can be compared with the results obtained by studies using the units of uterine activity integral if the latter is divided by 900. Gibb *et al.* (1984) studying uterine activity in nulliparous Chinese women reported a median level equivalent to a MAP of 1·6 kPa in the active phase of the first stage of labour. This value is very similar to our result of 1·5 kPa. Arulkumaran *et al.* (1984) recorded a lower level of activity, a median equivalent to 1·25 kPa, for parous patients in the active phase of the first stage. Again this is very similar to the result of 1·22 kPa obtained for parous patients in our study. Steer *et al.* (1984) failed to detect any significant parity difference in the first stage uterine activity and their mean value for all patients was 1·22 kPa. The difference between our results and those of Steer *et al.* (1984) are difficult to explain, particularly as

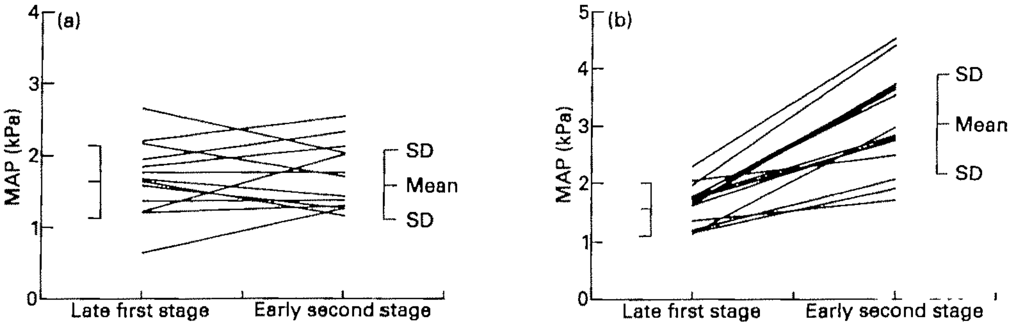

Fig. 1. (a) A comparison of MAP in the last 15 min of the first stage with MAP in the first 15 min of the second stage in the absence of second stage maternal pushing efforts (n = 13, paired t-test $P>0·05$); (b) A comparison of MAP in the last 15 min of the first stage with MAP in the first 15 min of the second stage in the presence of second stage maternal pushing efforts (n = 16, paired t-test $P<0·001$).

variables such as maternal height, cervical dilatation at the onset of labour and mode of analgesia were similar. The mean duration of labour was shorter in our study. Perhaps we were investigating more efficient labours.

It has been shown that epidural analgesia has no effect on the rate of cervical dilatation in spontaneous labour (Studd *et al.* 1980) or on the level of uterine activity, provided adrenaline is not added to the local anaesthetic solution used (Jouppila *et al.* 1977). We found that epidural analgesia was associated with a longer duration of both the first and the second stage. This does not imply that an epidural causes labour to be prolonged. In our study, analgesia was not allocated randomly but was determined primarily by patient preference. Epidural analgesia is often given to patients whose labour is prolonged or difficult and it is likely that the two analgesic groups studied are not comparable. Despite this reservation, it is interesting to note that for the first stage of labour, within each parity group, there was no difference in uterine activity comparing epidural patients with pethidine/Entonox patients. Furthermore, administration of epidural analgesia did not seem to have any short-term effect on any measure of uterine activity.

Bates *et al.* (1985) investigated uterine activity at the onset of the second stage in the absence of maternal pushing efforts. The uterine activity integral was significantly lower for patients given epidural analgesia compared with patients given pethidine or Entonox. In our study, uterine activity was measured for the whole of the second stage including periods of pushing. Despite these differences in method, we also recorded a lower level of uterine activity (MAP, contraction frequency and MCAP) in patients with epidural analgesia.

Gibb *et al.* (1984) observed a marked rise in uterine activity immediately after intrauterine catheter insertion, and attributed it to the local release of prostaglandins. We looked for a similar phenomenon in our population. The MAP in the first 15 min after catheter insertion was compared with the MAP in the second 15 min after catheter insertion. No significant difference could be found. Furthermore, there was no difference between the MAP in the first 15 min after catheter insertion and the whole of the first third of the first stage.

Gibb *et al.* (1984) and Arulkumaran *et al.* (1984) related the level of uterine activity to cervical dilatation and noted a sharp increase at 9 cm. Steer *et al.* (1984) using the same method of data analysis observed a steady rise in uterine activity from 4 to 10 cm and no sudden increase at 9 cm. It is difficult to compare these studies with our findings as we employed a different method of data analysis. We divided the first stage into three equal time intervals and calculated the MAP for each third. Certainly we noted a rise in the level of uterine activity over the course of the first stage particularly in parous patients but it is not possible to say how this rise related to cervical dilatation.

We have observed levels of uterine activity in spontaneous labour similar to those reported using other methods of data collection. The advantage of our system lies in its ability to derive various measures of uterine activity over any time interval desired. We believe that the use of microcomputers to measure and analyse these variables will increase our understanding of myometrial activity and lead to improvements in the management of labour, particularly abnormal labour.

References

Arulkumaran, S., Gibb, D M. F., Lun, K C , Heng, S H & Ratnam, S S (1984) The effect of parity on uterine activity in labour *Br J Obstet Gynaecol* **91**, 843-848

Bates, R G , Helm, C W., Duncan, A. & Edmonds, D. K. (1985) Uterine activity in the second stage of labour and the effect of epidural analgesia *Br J Obstet Gynaecol* **92**, 1246-1250.

Crawford, J W. (1975) Computer monitoring of fetal heart rate and uterine pressure. *Am J Obstet Gynecol* **121**, 342-350.

Gibb, D. M. F., Arulkumaran, S., Lun, K C. & Ratman, S S. (1984) Characteristics of uterine activity in nulliparous labour. *Br J Obstet Gynaecol* **91**, 220-227.

Jouppila, P , Jouppila, R., Kaar, K & Merila, M. (1977) Fetal heart rate patterns and uterine activity after segmental epidural analgesia. *Br J Obstet Gynaecol* **84**, 481-486.

Phillips, G. F & Calder, A A. (1987) Units for the evaluation of uterine contractility. *Br J Obstet Gynaecol* **94**, 236-241.

Steer, P J. (1977) The measurement and control of uterine contractions. In *The Current Status of Fetal Heart Rate Monitoring and Ultrasound in Obstetrics*. Royal College of Obstetricians and Gynaecologists, London, pp. 48-68

Steer, P. J., Carter, M. C , Gordon, A. J. & Beard, R. W (1978) The use of catheter-tip pressure trans-

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Doppler echocardiographic assessment of atrioventricular velocity waveforms in normal and small-for-gestational-age fetuses

GIUSEPPE RIZZO, DOMENICO ARDUINI, CARLO ROMANINI, SALVATORE MANCUSO

Summary. A prospective longitudinal study determined the physiological patterns of blood flow velocity waveforms in normal and in small-for-gestational-age (SGA) fetuses. Using a Pulsed Doppler Duplex system, 125 normally grown fetuses and 35 SGA fetuses were studied longitudinally at between 27 and 42 weeks gestation. In normal fetuses the ratio between the E velocity (early passive ventricular filling) and the A velocity (active ventricular filling during atrial contraction) increased progressively during pregnancy in both transmitral and transtricuspid waveforms, approaching 1 at term. In SGA fetuses, the E/A ratios did not increase during pregnancy and the values obtained were significantly lower than in normal fetuses. The ratio between the transtricuspid and transmitral mean temporal velocities remained almost constant throughout pregnancy in the normal fetuses with transtricuspid velocity slightly exceeding the transmitral velocity. On the other hand, in SGA fetuses the ratio between the mean temporal velocities was inversed with the transmitral velocity progressively greater than the transtricuspid velocity suggesting the existence of intracardiac haemodynamic changes in these fetuses.

With the advent of Doppler ultrasound techniques there has been an increased interest in the estimation of fetal blood flow (Eik-Nes *et al.* 1980; Campbell *et al.* 1983). More recently range-gated pulsed Doppler ultrasound techniques have enabled human fetal intracardiac blood flow to be examined. Up to now fetal Doppler echocardiography has been used mainly to diagnose structural and functional heart disease prenatally (Maulik *et al.* 1985; Silverman *et al.* 1985; Crawford *et al.* 1986), and few data (Meijboom *et al* 1985) are available on intracardiac haemodynamic changes during fetal development

We set up a longitudinal prospective study to assess the normal pattern of intracardiac blood flow velocity waveforms and compare these with the patterns found in small-for-gestational-age (SGA) fetuses.

Subjects and methods

The normal control group comprised 125 healthy pregnant women referred to the ultrasound laboratory of our institution who were studied longitudinally with intracardiac Doppler

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Department of Obstetrics and Gynaecology, Universitá Cattolica S. Cuore, Rome, Italy
GIUSEPPE RIZZO
DOMENICO ARDUINI
SALVATORE MANCUSO

Department of Obstetrics and Gynaecology, Universitá di Ancona, Italy
CARLO ROMANINI

Correspondence. Dr Giuseppe Rizzo, Ist Cl. Ostetrica e Ginecologica, Universitá Cattolica S. Cuore, Largo A Gemelli, 8, 00168 Rome, Italy

ultrasound at four gestational ages: 27–30, 31–34, 35–38 and 39–42 weeks. In addition 35 patients with SGA fetuses were studied. The criteria for defining SGA were an abdominal circumference below the 10th centile according to the nomograms of Campbell & Thoms (1977), and postnatal confirmation by a birthweight under the 10th centile for an Italian population (Gagliardi *et al.* 1975).

All patients gave their informed consent to participate in the study. All pregnancies were singleton, each patient was certain of her last menstrual period and the gestational age was confirmed by early second trimester ultrasound examination.

Recordings were performed in a quiet room with the patient lying in a comfortable semi-recumbent position, and during a period of fetal rest without breathing movements. A pulsed Doppler Duplex ultrasound system (Ansaldo AUC 940) with 3·5 and 5 MHz convex transducers was used. The Doppler carrier frequency ranged from 2·4 to 5 MHz. In this investigation we recorded the blood flow velocity waveforms over the atrioventricular (AV) valves as described by Meijboom *et al.* (1985). Briefly, a four-chamber view of the fetal heart was obtained and the AV values were easily identified. Doppler sample volume was then placed immediately below either the mitral or tricuspid valves (Fig. 1) and velocity waveforms were recorded. Thus the angle of insonation was near 0° and we avoided the underestimation of velocities.

The AV velocity waveforms obtained showed a characteristic biphasic pattern. The early phase (E peak) represents the passive venous filling of the ventricle, whereas the late phase (A peak) represents the active ventricular filling during atrial contraction (Fig. 2).

Permanent records of all velocity waveforms were obtained with a strip chart recorder for later analysis. Recordings obtained using an angle of Doppler beam insonation larger than 20° were rejected. The sonographic print-outs were subjected to waveform analysis using the digitizing tablet of a microcomputer (Cardio 80, Kontron). We calculated the E peak and A peak velocities and the mean temporal velocity (MTV) over 10 consecutive cardiac cycles. The ratio between the E and A velocities (E/A ratio) in both AV valves and the ratio between the transtricuspid and transmitral MTV were then calculated. All data are expressed as mean (SD) values. Statistical analysis used one-way analysis of variance and the unpaired *t*-test.

Results

A total of 496 recordings were obtained, 86 were from SGA fetuses (SGA group) and 410 from

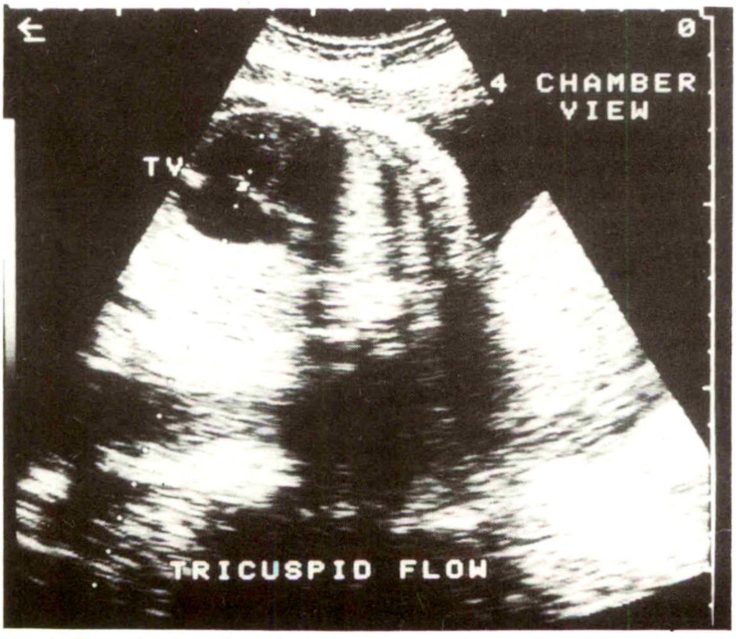

Fig. 1. Four chamber view of the fetal heart. The sample volume was placed immediately below the tricuspid valve.

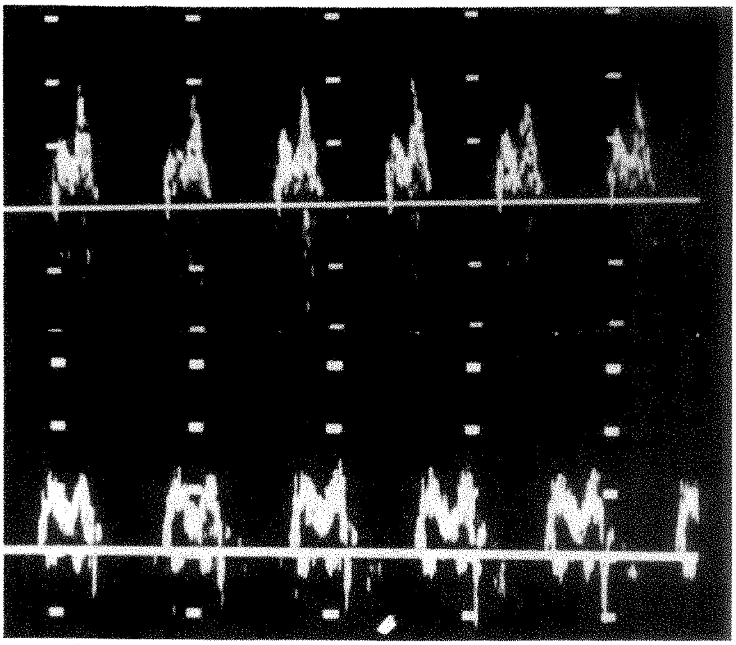

Fig. 2. Example of transmitral velocity waveforms at 27 weeks (upper tracing) and at term (lower tracing).

fetuses with a normal birthweight (control group). The distribution of recordings by gestational age-group is shown in Table 1. All the fetuses in the control group had a birthweight greater than the 25th centile. Of the 35 fetuses in the SGA group 20 (57%) had a birthweight between the 5th and 10th centile and 15 (43%) had a birthweight below the 5th centile.

Reliable assessment of velocity waveforms was obtained in 90·4% and 89·8% of the recordings over the mitral and tricuspid valves, respectively.

To determine interobserver variability, echocardiographic recordings of 20 fetuses were performed consecutively by two experienced observers. The correlation coefficients for all the variables measured were excellent with a value of over 0·89.

Fetuses characterized by a normal birthweight (control group) showed in both the AV valves a progressive increase in the E/A ratio which at term approached 1 (Figs 3 & 4). One-way analysis of variance showed these trends in the E/A ratio to be statistically significant both in the transmitral ($F = 4{\cdot}3$, $P<0{\cdot}01$) and the transtricuspid ($F = 4{\cdot}1$, $P<0{\cdot}01$) waveforms. In the control group the ratio between the transtricuspid and the transmitral MTV remained almost constant throughout pregnancy with the transtricuspid MTV slightly higher than the transmitral MTV.

Table 1. Distribution of echocardiographic recordings by gestational age

	Gestation (weeks)			
Group	27–30	31–34	35–38	39–42
Normal fetuses	125	122	98	65
SGA fetuses	32	35	19	0

SGA, Small-for-gestational-age.

Conversely, in the SGA group the E/A ratios did not increase during pregnancy and the values were significantly lower than those obtained in the control group (unpaired *t*-test) (Figs 3 & 4). Moreover in the SGA group the ratio between the transtricuspid and the transmitral MTV was inversed, with the transmitral MTV progressively greater than the transtricuspid MTV (Fig. 5).

Discussion

Our results confirm the feasibility of recording intracardiac blood flow in the human fetus. Velocity waveforms over AV valves are readily detected in a high proportion of examinations and the excellent level of interobserver agree-

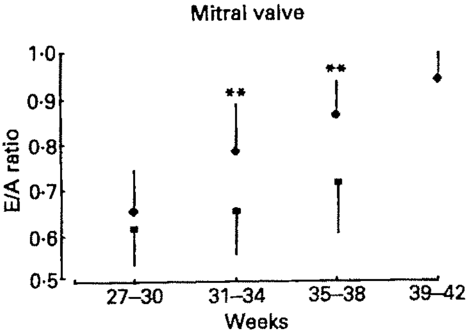

Fig. 3. Changes in transmitral E/A ratio in normal (◆) and small-for-gestational-age (SGA) (■) fetuses. $^{**}P<0\cdot001$ (unpaired t-test)

ment demonstrates the reproducibility of the results. Moreover, the ability to obtain waveform profiles with an angle of insonation near 0° minimizes the errors of angle correction in velocity calculations. Normal fetuses showed a progressive increase in the E/A ratio on each side of the heart. These findings are in agreement with the results reported previously by Meijboom *et al.* (1985). The significance of this development is still obscure, but it is possible that the E/A ratio is influenced by myocardial compliance as well as by cardiac preload and afterload. Experimental studies (Romero *et al.* 1972) have demonstrated that the fetal heart is less compliant than the postnatal myocardium. These findings could explain the dominance of the atrial phase (A peak) during intrauterine life. Moreover, cardiac preload, represented by venous return flow, and afterload, mainly due to peripheral vascular resistance (Rudolph 1985), can both influence waveform profiles As demonstrated in experimental animals (Dawes 1968) and in the human fetus (Trudinger *et al.* 1985), placental vascular resistance falls progressively during mid and late pregnancy and that could influence cardiac preload and afterload. The variation in the E/A ratio throughout pregnancy could also be related to the progressive decrease of placental impedance characterizing normal pregnancies. The presence of shunts in the fetal circulation such as foramen ovale and ductus arteriosus may explain the similar trend found on the two sides of the heart.

In SGA fetuses the E/A ratio is lower than in fetuses with normal birthweights and an increase in the A phase is particularly evident. These modifications could be related either to the

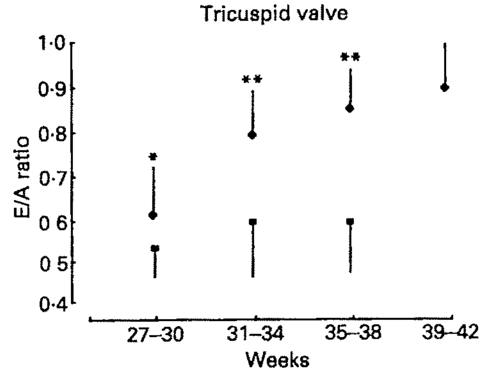

Fig. 4. Changes in transtricuspid E/A ratio in normal (◆) and small-for-gestational-age (SGA) (■) fetuses $^{*}P<0\cdot05$, $^{**}P<0\cdot001$ (unpaired t-test)

decrease of cardiac compliance or to the characteristic increase of placental resistance of these fetuses (Trudinger *et al.* 1985) which might affect cardiac preload and afterload.

In normal fetuses the ratio between the transtricuspid and transmitral MTV remains almost constant with the transtricuspid MTV somewhat greater. We did not estimate absolute cardiac output as during prenatal life this measurement is prone to errors contributed by inaccuracies in the calculation of valve area. From our data, therefore, a dominance of right cardiac output cannot be established.

None the less, it is notable that in SGA fetuses the transmitral MTV exceeds the transtricuspid MTV. SGA fetuses are characterized by a redistribution of blood flow with an increased perfusion to the brain and myocardium and an increase of vascular resistance at the level of the descending aorta and placental bed. In this condition of 'brain sparing' the left heart is presented with the reduced resistance of the

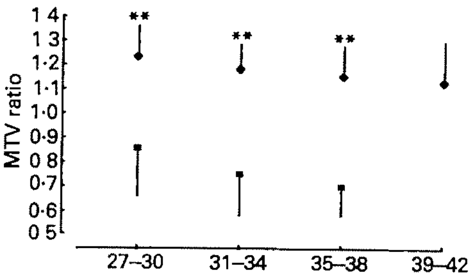

Fig. 5. Changes in transtricuspid/transmitral mean temporal velocities (MTV) in normal (◆) and small-for-gestational-age (SGA) (■) fetuses $^{**}P<0\cdot001$ (unpaired t-test)

coronary arteries and of head and neck arteries (Wladimiroff *et al.* 1986; Arduini *et al.* 1987), whereas the right heart, ejecting through the ductus arteriosus into the descending aorta, is presented with an increased vascular resistance (Jouppila & Kirkinen 1984; Rizzo *et al.* 1987). Therefore such selective changes of cardiac afterload could alter the output of the two ventricles and explain the high values of transmitral MTV found in SGA fetuses.

Our data suggest that there are intracardiac haemodynamic changes in SGA fetuses compared with normal fetuses. These results justify further studies on the clinical significance of intracardiac echocardiography in the early diagnosis and monitoring of SGA fetuses.

References

Arduini, D., Rizzo, G., Romanini, C. & Mancuso, S. (1987) Fetal blood flow velocity waveforms as predictors of growth retardation. *Obstet Gynecol* **70**, 7-10.

Campbell, S. & Thoms, A. (1977) Ultrasound assessment of the fetal head of abdominal circumference ratio in the assessment of growth retardation. *Br J Obstet Gynaecol* **84**, 165-171.

Campbell, S , Griffin, D. R , Pearce, J M , Diaz-Recanses, J., Cohen-Overbeek, T. E. & Willson, K. (1983) New Doppler technique for assessing uteroplacental blood flow. *Lancet* **i**, 675-677.

Crawford, D C , Chita, S & Allan, L. D. (1986) The value of Doppler in the prenatal evaluation of congenital heart disease. In *Obstetric and Neonatal Blood Flow,* BES Conference, London

Dawes, G. S. (1968) The umbilical circulation. In *Fetal and Neonatal Physiology,* Year Book Publishers, Inc , Chicago, pp. 66-78.

Eik-Nes, S. H., Brubakk, A O. & Ulstein, M K (1980) Measurement of human fetal blood flow. *Br Med J* **280**, 283-284.

Jouppila, P & Kirkinen, P. (1984) Increased vascular resistance in the descending aorta of the human fetus in hypoxia *Br J Obstet Gynaecol* **91**, 853-856

Gagliardi, L., Preve, C. U., Corduro di Montezemolo, C , Nattone, G. P & Piazza, A. (1975) Accrescimento intrauterino ed eta' gestazionale in un campione di 9774 casi. *Ann Ostet Ginecol Med Perinat* **96**, 147-158.

Maulik, D., Nanda, N. C , Moodley, S., Saini, V D. & Thiede, H. A. (1985) Application of Doppler echocardiography in the assessment of fetal cardiac disease *Am J Obstet Gynecol* **151**, 951-957.

Meijboom, E J., De Smedt, M. C H., Visser, G. H A., Jager, W., Bossina, K. K. & Huisijes, H. J (1985) Cross-sectional Doppler echocardiographic evaluation of the fetal cardiac output during the second and third trimester of pregnancy· a longitudinal study In *The Physiological Development of the Fetus and Newborn* (Jones, C. T. & Nathanielsz, P. W., eds), Academic Press Inc. Ltd, London, pp 749-752

Rizzo, G., Arduini, D., Pennestri', F., Romanini, C & Mancuso, S (1987) The fetal behaviour in growth retardation. its relationships to fetal blood flow *Prenat Diagn* **7**, 229-238.

Romero, T , Covell, J. & Friedman, W. F (1972) A comparison of pressure-volume relations of the fetal, newborn and adult heart. *Am J Physiol* **222**, 1285-1290.

Rudolph, A. (1985) Distribution and regulation of blood flow in the fetal and neonatal lamb. *Circ Res* **57**, 811-821.

Silverman, N H , Kleinman, C S , Rudolph, A M., Copel, J. A., Weinstein, E. M., Enderlein, M. A. & Golbus, M (1985) Fetal atrioventricular valve insufficiency associated with nonimmune hydrops: a two dimensional echocardiographic and pulsed Doppler ultrasound study. *Circulation* **72**, 825-832.

Trudinger, B. J , Giles, W. B., Cook, C M., Bombardieri, J. & Collins, L (1985) Fetal umbilical artery flow velocity waveforms and placental resistance: clinical significance. *Br J Obstet Gynaecol* **92**, 23-30.

Wladimiroff, J. W., Tonge, H M & Stewart, P A (1986) Doppler ultrasound assessment of cerebral blood flow in the human fetus *Br J Obstet Gynaecol* **93**, 471-475.

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Pulmonary metastases in gestational trophoblastic disease: a review of 97 cases

JOTHI KUMAR, A. ILANCHERAN, S. S. RATNAM

Summary. Metastatic gestational trophoblastic disease poses problems in diagnosis and management and has a poorer prognosis than the non-metastatic variant. The lung is the most common site of metastases. This paper reviews 97 patients with pulmonary metastasis developing after gestational trophoblastic disease who were seen at one centre over 26 years. Most patients had an antecedent molar pregnancy but an associated choriocarcinomatous lesion in the uterus was absent in the majority. In many patients the pulmonary lesion was asymptomatic. Whilst chemotherapy was the treatment of choice, selective thoracotomy in cases with solitary lung nodules reduced the treatment time and need for aggressive multi-drug combination regimens. The overall survival rate at 2 years after diagnosis was 65%. A higher mortality was found when the antecedent pregnancy ended at term, when the time interval between the preceding pregnancy and diagnosis of pulmonary metastases was >1 year, when multiple pulmonary secondaries were present or when cerebral metastases occurred. The main causes of death were cerebral haemorrhage, respiratory failure and pulmonary embolism.

Metastatic gestational trophoblastic disease poses problems in diagnosis and management. Whilst the non-metastatic disease has an almost uniformly good prognosis with cure rates approximating 100% in many centres, the metastatic variant still has a relatively poorer prognosis.

The lung is the commonest site of spread. This would appear to be fortunate as the lung is most accessible radiologically and hence earlier and easier diagnosis can be achieved. Furthermore, solitary pulmonary secondaries, persisting despite initial chemotherapy, can be removed surgically without much difficulty

The purpose of this paper is to review patients with gestational trophoblastic disease seen in our department, who developed pulmonary metastases, and to examine some of the factors that may have affected prognosis.

Subjects and methods

Case notes of 988 consecutive patients with gestational trophoblastic disease admitted between 1959 and 1984 were examined. The cases were classified according to the definitions formulated by the World Health Organization (1983) and the notes of the patients with pulmonary metastases were examined in greater detail

Results

Distribution of cases

The total number of cases and their distribution is shown in Table 1. Of the 988 patients reviewed, 127 were recorded as having meta-

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Department of Obstetrics and Gynaecology, National University of Singapore, Lower Kent Ridge Road, Singapore 0511
JOTHI KUMAR *Lecturer*
A. ILANCHERAN *Senior Lecturer*
S S RATNAM *Professor and Head*

Correspondence: Dr Jothi Kumar, Centre of early Human Development, c/o Department of Obstetrics and Gynaecology, Monash Medical Centre, 246 Clayton Road, Clayton, Victoria 3168, Australia

Table 1. Classification of 988 patients with gestational trophoblastic disease and frequency of pulmonary metastases (1959–1984)

Type*		Pulmonary metastases	
		Present	Absent
Gestational trophoblastic disease	988	—	—
Hydatidiform mole	820	—	—
Invasive mole	40 (23·8%)	16	24
Choriocarcinoma	30 (17·9%)	22	8
Gestational trophoblastic tumour	98 (58·3%)	59	39
Total	168 (100%)	97	71†

* Classification according to World Health Organization (1983)

† Thirty of these patients had metastatic disease but no pulmonary lesions.

stases, of which 97 (76·4%) included pulmonary lesions. Other sites of metastases were the vagina (22), brain (14), ovary and vulva (4 each), liver and intestine (3 each), fallopian tubes (2) and one case each in the pancreas, spleen, ureter, brachial plexus, cheek, eye and ililac crest.

Of the 97 patients with pulmonary metastases, the metastases were confined to the lungs alone in 57, and in the remaining 40 patients there were also metastases at other sites: the uterus (27), brain (12), vagina (11), vulva (4), liver (3) and others (8). Of the 14 patients in our overall series with cerebral metastases, all but two also had pulmonary lesions.

Table 1 shows that of the 97 patients with pulmonary metastases, 59 (61%) had gestational trophoblastic tumour, 16 (17%) had invasive mole and 22 (23%) had choriocarcinoma. Conversely, pulmonary metastasis developed in 59 of 98 (60·2%) of patients with trophoblastic tumour, in 16 of 40 (40%) of those with invasive mole, and in 22 of 30 (73%) of those with choriocarcinoma.

The age of the patients ranged between 15 and 53 years, the largest proportion (47%) were between 21 and 30. The highest parity was 16 and 75% were multiparous. There was no racial predeliction in the series.

Antecedent pregnancy

In the pregnancy preceding diagnosis of pulmonary metastases 87% had a molar pregnancy; 4% a term pregnancy; 4% an abortion and 1% an ectopic pregnancy (Table 2).

In the patients with an antecedent molar pregnancy, 62 (74%) of the lesions were diagnosed within 6 months; where the preceding pregnancy was normal or ended in abortion the lesion tended to be diagnosed between 1 and 2 years afterwards. However, one patient with a molar pregnancy had a pulmonary lesion diagnosed 12 years later and as many as 11 were diagnosed 2–6 years after a preceding molar pregnancy.

Table 2. Antecedent pregnancy and interval to diagnosis with 2-year survival status in 97 patients with pulmonary metastases

		Interval between antecedent pregnancy and diagnosis (years)						Mortality
Antecedent pregnancy	*n* (%)	<0·5	0·5<1	1<2	2<6	12	Unknown	*n* (%)
Hydatidiform mole	84 (86·6)	62	4	6	11	1	0	15 (17·9)
Term pregnancy	4 (4·1)	0	0	1	0	0	3	2 (50·0)
Abortion	4 (4·1)	1	0	1	0	0	2	1 (25·0)
Ectopic pregnancy	1 (1·1)	1	0	0	0	0	0	0 (0·0)
Unknown	4 (4·1)	0	0	0	0	0	4	1 (25·0)
Total	97 (100·0)	63	4	8	11	1	9	19

Table 3. Modes of treatment of pulmonary metastatic disease

	Patients		Mortality	
	n	(%)	*n*	(%)
Chemotherapy alone	46	(47·4)	9	(19·6)
Chemotherapy + total hysterectomy with or without BSO	35	(36·0)	5	(14·3)
Chemotherapy +thoracotomy	13	(13·5)	2	(15·4)
No treatment*	3	(3·1)	3	(100)
Total	97	100	19	

* These three patients had a primary hysterectomy for hydatidiform mole and subsequently developed pulmonary metastases with raised hCG levels, they died before treatment.

BSO, Bilateral salpingo-oophorectomy

Other features

Only four of the patients with pulmonary metastases had symptoms—either chronic cough and/or haemoptysis. All the other patients were diagnosed on the basis of chest radiographs. None complained of breathlessness as a presenting symptom. A solitary lung lesion was present in only 12 of the 97 patients, the other 85 (88%) had multiple pulmonary nodules radiologically at the time of diagnosis.

Therapy

Therapeutic regimens changed significantly during the period under review. In the first 10 years of this series, methotrexate (MTX) alone was most frequently used. Subsequently, multi-agent chemotherapy using MTX and actinomycin-D was the mainstay of therapy. Occasionally other drugs such as 6-mercaptopurine were used.

Thirty-five of the patients had a hysterectomy either at the initial diagnosis of antecedent pregnancy or subsequently (Table 3). Mortality rates were not affected by the hysterectomy. Thirteen patients had a thoracotomy for persistence of solitary lung nodules despite intensive chemotherapy and the absence of metastases elsewhere (Table 4). Histology of the excised lung lesions showed active tumour in seven of them. One patient had a second thoracotomy 10 months after the first operation and she is presently well.

Survival

The survival of the patients was analysed at the end of 2 years after diagnosis of pulmonary metastases because earlier in the series the patients were treated before radioimmunoassay of β-human chorionic gonadotrophin (β-hCG) was established and recurrence of disease after this period is very uncommon.

The overall survival rate of the 97 patients was 64·9%, 19 (20%) died and 15 (16%) were lost to follow-up. As expected, survival was poorer in patients where pulmonary metastases developed after a term pregnancy or abortion (Table 2), and was related to the time interval between the antecedent pregnancy and diagnosis of pulmonary metastatic disease (Table 5).

Of the 19 deaths in the series, the majority occurred within a year of diagnosis (Table 6). Except for four patients who had a post-mortem, the cause of death was determined on clinical grounds The main cause was cerebral haemorrhage, other causes were respiratory failure and pulmonary embolism. There was no death related to sepsis or to drug toxicity. Except for one patient whose chest radiograph showed a solitary metastasis the others who died had multiple lung nodules and 17 had extra-pulmonary disease.

Cerebral metastases were associated with an extremely high mortality rate (Table 6). Nevertheless, one patient who had both lung and brain secondaries is presently alive and well, after two

Table 4. Clinical features in 13 patients who had a thoracotomy

Number of patients	13
Lung metastases alone	7
Associated lesions	
Uterus	3
Others	3
Interval between diagnosis and operation (months)	
2–4	8
5–7	3
9	2
Histology of lung metastases	
Choriocarcinoma	7
Undetermined	6
Second thoracotomy	1
Two-year survival status	
Alive	11
Dead	2*

* Cause of death, cerebral haemorrhage.

Table 5. Interval from antecedent pregnancy to diagnosis of pulmonary metastases related to 2-year survival status

Interval (years)	Alive (*n*)	Dead (*n*)	Unknown (*n*)
<0·5	56	5	3
0·5<1	2	1	1
1<2	3	4	1
2<4	2	3	2
4–6	0	2	2
12	0	1	0
Unknown	0	3	6
Total	63	19	15

successful craniotomies for cerebral bleeding from the secondaries.

Discussion

Our review has confirmed that in patients with gestational trophoblastic disease and pulmonary metastases, survival is affected by the time interval between diagnosis of the metastases and the antecedent pregnancy, by the presence of metastases at sites other than the lungs especially the brain, and by whether the antecedent pregnancy was molar.

The higher mortality rate associated with an antecedent normal pregnancy can in part be explained by the delay in diagnosis of unexpected trophoblastic disease in such patients (Novak & Seah 1954; Park & Lees 1950). Whereas pulmonary metastases were usually diagnosed within 4 months after a molar pregnancy, those following a term pregnancy were generally diagnosed after 1 year. Choriocarcinoma occurring after a term pregnancy is also prone to more extensive metastatic spread and is less responsive to conventional therapy (Adelye *et al* 1980; Miller *et al.* 1979).

The principal treatment for gestational trophoblastic disease is chemotherapy. Earlier in our series methotrexate was the primary single agent used, and the commonest combination regimen was methotrexate and actinomycin-D in conventional doses, 6-mercaptopurine was used occasionally. The CHAMOCA regimen of Bagshawe was rarely used. Since the beginning of 1979, patients with pulmonary metastases who did not respond to methotrexate alone were treated with moderate dose methotrexate and actinomycin-D with folinic acid rescue (Ratnam & Ilancheran 1982) with good results. More recently, patients with very extensive pulmonary metastases and at high risk of, or proven, cerebral metastases have been treated with etoposide in addition to methotrexate and actinomycin-D (EMA regimen) as this provides an effective concentration of drug to the central nervous system (Athanassiou *et al.* 1983).

While chemotherapy remains the mainstay of treatment, surgery has a role in the management of selected patients (Shirley *et al.* 1971; Sink *et al.* 1981; Ratnam & Ilancheran 1982) particularly in those with solitary lung metastasis resistant to chemotherapy who have no lesions elsewhere.

Notably, hysterectomy, particularly earlier in the series, did not significantly reduce mortality rates (Table 3). In fact, only 28% had an identifiable lesion in the uterus. Absence of a uterine lesion associated with extensive metastatic disease has been reported elsewhere (Hertz 1978; Ober 1969; Tow 1967).

The role of hysterectomy currently would appear to be similar to that of thoracotomy in the extirpation of the solitary, identifiable lesion resistant to aggressive chemotherapy.

Trophoblastic embolization to the lungs which is common even in normal pregnancies (Johnson *et al.* 1979) is the most obvious explanation why the lungs are the most frequent site of metastases in gestational trophoblastic disease (Bagshawe

Table 6. Clinical features in 19 patients who died with pulmonary metastatic disease

Number of deaths	19
Interval between diagnosis and death (years)	
<1	14
1–2	4
>4	1
Treatment	
Chemotherapy alone	9
Chemotherapy + surgery	7
No treatment	3
Metastatic spread	
Lung alone	2
Lung + brain	9
Lung + other sites	8
Cause of death	
Cerebral haemorrhage	9 (47·4%)
Respiratory failure	3 (15·8%)
Pulmonary embolism	1 (5·3%)
Unknown	6 (31·5%)

1969; Novak & Seah 1954; Park & Lees 1950). In our series, the incidence of pulmonary metastases was 76%. Most of these lesions were asymptomatic and were diagnosed radiologically, and although haemoptysis, dyspnoea, pleuritic pain and haemothorax are reported symptoms of pulmonary metastases (Bagshawe 1969; Johnson *et al* 1979) they were not often seen. It is clearly necessary to diagnose these lesions earlier, and although many follow-up regimens include frequent chest radiographs until hCG levels are undetectable by radioimmunoassays (Ratnam & Ilancheran 1982), the place of computerized axial tomography (CAT) scans in the routine management of trophoblastic tumours to detect very early pulmonary metastases needs to be defined Certainly, any chest radiograph showing multiple nodules in a young woman should raise suspicion of metastatic gestational trophoblastic disease and appropriate steps taken to exclude or confirm the diagnosis.

Although a higher mortality rate (21%) was seen with multiple pulmonary metastases, 8% of the patients with solitary lung nodules also died. Hence the patient with a single lung lesion cannot be viewed with complacency.

The patient with multiple pulmonary metastases is at risk of developing brain metastases (World Health Organization 1983). There is some risk even in the absence of identifiable pulmonary metastases. Although 12 of the 14 patients with cerebral metastases also had lung metastases, the other two did not have demonstrable secondaries on the chest radiograph. The majority of the patients with pulmonary metastases died of cerebral haemorrhage (Table 6). It is known that chemotherapy may cause rapid necrosis of brain metastases with resultant intracerebral haemorrhage (World Health Organization 1983). Higher doses of chemotherapy, as in the EMA regimen, are thought to be both haemostatic and tumoricidal. Whilst we do not believe in prophylactic intra-thecal methotrexate, we search carefully for cerebral metastases with a CAT scan, which we have had since the late 1970s. Currently, patients with proven brain metastases are treated by whole brain irradiation and EMA chemotherapy.

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References

Adelye, J A , Osinusi, B O & Adewunmi, O. A. (1980) Malignant trophoblastic disease Review of 21 deaths. *Singapore J Obstet Gynecol* **11,** 59-61

Athanassiou, A , Begent, R H., Newlands, E. S , Parker, D., Rustin, G. J. & Bagshawe, K D. (1983) Central nervous system metastases of choriocarcinoma: 23 years experience at Charing Cross Hospital. *Cancer* **52,** 1728-1735.

Atwood, H. D. & Park, W W. (1961) Embolism to the lung by trophoblast *J Obstet Gynaecol Br Commonw* **68,** 611-617

Bagshawe, K D. (1969) *Choriocarcinoma—the Clinical Biology of the Trophoblast and its Tumour* Edward Arnold, London, pp. 93-103

Hertz, R. (1978) *Choriocarcinoma and Related Gestational Trophoblastic Tumours in Women* Raven Press, New York, pp. 140-141.

Johnson, T R , Comstock, C H & Anderson, D G. (1979) Benign gestational trophoblastic disease metastatic to the pleura· unusual case of hemothorax. *Obstet Gynecol* **53,** 509-511

Miller, J M , Surwit, E. A. & Hammond, C B (1979) Choriocarcinoma following term pregnancy. *Obstet Gynecol* **53,** 207-212

Novak, E. & Seah, C S (1954) Choriocarcinoma of the uterus—a study of 74 cases from the Mathieu Memorial Chorioepithelioma Registry *Am J Obstet Gynecol* **67,** 933-961.

Ober, W B (1969) The pathology of choriocarcinoma *Ann N Y Acad Sci* **172,** 279-282

Park, W W & Lees, J C (1950) Choriocarcinoma· a review and analysis of 516 cases *Arch Path* **49,** 73-104.

Ratnam, S. S & Ilancheran, A (1982) Disease of the trophoblast *Clin Obstet Gynaecol* **9,** 539-564

Ratnam, S. S & Ilancheran, A. (1982) Surgery in metastatic trophoblastic disease *Semin Oncol* **9,** 221-223

Shirley, R. L , Goldstein, D. P & Collins, J J. (1971) The role of chemotherapy in management of patients with chest metastases from gestational trophoblastic disease *J Thorac Cardiovasc Surg* **63,** 545-550.

Sink, J. D , Hammond, C D. & Young, W. G Jr (1981) Pulmonary resection in the management of metastases from gestational choriocarcinoma *J Thorac Cardiovasc Surg* **81,** 830-834

Tow, S H (1967) The pulmonary lesion in choriocarcinoma *Proc Royal Soc Med* **60,** 239-240

World Health Organization (1983) *Gestational Trophoblastic Disease* Report of a WHO Scientific Group Technical Report Series 692, WHO, Geneva, pp. 10-13.

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A study comparing transcervical with transabdominal chorionic villus sampling (CVS)

WILLIAM E. MACKENZIE, DEBORAH S. HOLMES, JOHN R. NEWTON

Summary. Chorionic villus sampling (CVS) was performed in 50 anaesthetized patients before therapeutic abortion by the transabdominal route and then by the transcervical route. The two methods of villus sampling were equally successful in obtaining villi but the transcervical method was significantly better at obtaining chorionic villi >10 mg in weight (χ^2 13·92 $P<0·001$). Placental position did not affect villus recovery with either sampling method.

Transabdominal chorionic villus sampling may have advantages compared to transcervical chorionic villus sampling (CVS) which involves vaginal manipulations, the passage of a cannula through an endocervix that is contaminated with bacteria and restricted manoeuverability of the cannula within the uterine cavity. Transabdominal sampling allows freer access to the placental site, has less potential for introducing infection and no vaginal manipulations are necessary. Despite these theoretical advantages only 1·5% of all diagnostic CVS procedures recently reported from 92 centres by Laird Jackson (*Chorionic Villus Sampling Newsletter* 1986) were performed by the transabdominal route. In a recent study which compared transabdominal and transcervical CVS, villi were successfully obtained in 98% of patients using the transabdominal method, but only 52% of samples were successfully karyotyped using a direct preparation technique (Bovicelli *et al* 1986). This was attributed to the low villus weights obtained transabdominally compared to the higher weights obtained by the transcervical method (with an 82% success in direct chromosome preparation). If small villus samples were found to be characteristic of transabdominal CVS (Brambati *et al.* 1986) then not only would chromosome analysis by direct preparation from villi be unreliable, but also biochemical and DNA analysis (Upadyaya *et al.* 1984). However, a report by Smidt-Jensen *et al.* (1986), who have the world's largest diagnostic series of transabdominal CVS, stated that an average of 30 mg of villi could be reliably obtained by this technique. We have assessed the efficacy of transabdominal compared with transcervical CVS in obtaining measured weights of villi and examined the effects of placental position on villus recovery using the two methods.

Academic Department of Obstetrics and Gynaecology, Birmingham Maternity Hospital, Edgbaston, Birmingham B15 2TG
WILLIAM E. MACKENZIE *Lecturer*
DEBORAH S HOLMES *Research Fellow*
JOHN R. NEWTON *Professor*

Correspondence: W E Mackenzie

Patients and methods

The study included 55 women who gave informed consent to participate. Local ethics committee approval was obtained. Four of the 55 women were excluded because preliminary ultrasonography did not show the presence of a live fetus. One twin pregnancy was excluded.

The remaining 50 women had a single, live fetus with a gestational age as assessed by ultrasound measurements ranging from 7+ to 13 weeks (mean 9·5 SD 1·1 weeks).

Experimental design

A single operator (W.E.M.) did all the sampling and in each patient sampling was attempted twice. Both the transabdominal and transcervical procedures were performed under general anaesthesia immediately before therapeutic termination of pregnancy. In order to avoid moving the patient excessively while under general anaesthesia, the transabdominal CVS was always performed first. To alleviate any bias in villus recovery that might arise, the placental site was first localized by ultrasound before sampling and both methods were used to sample only that site. Thus in cases where placental localization was uncertain no bias was given to the transcervical procedure following the known outcome of the first (transabdominal) sampling.

Ultrasound equipment

An ADR 4000 S/L ultrasound machine was used with a 3·0 MHz sector transducer in all cases.

Method of transabdominal CVS

One of us (W.E.M.) had gained experience of transabdominal CVS in Denmark using the Smidt-Jensen technique (Smidt-Jensen & Hahnemann 1984) Under continuous ultrasound guidance an 18-gauge 150 mm Spinal needle (Needle Industries, Redditch) was introduced into the uterus and just into the placental site. The trochar was removed and a 22-gauge 175 mm Spinal needle, with suction tubing attached, was inserted down the 18-gauge needle's cannula and into the placental site. With a rapid up and down motion of the 22-gauge needle the villi were cut before aspiration. Suction was applied from wall suction connected by plastic tubing (Vygon, Lectro-Cath, 1·5 mm in diameter) to the 22-gauge needle hub via a paediatric mucus aspirator and suction was controlled by an R90 plastic connection in which a small hole had been drilled to allow finger-tip control.

Visualization of the needle direction was facilitated by having a needle holder attached to the ultrasound transducer with a central slot down which the needle was passed. This contained a spring which gripped the needle allowing controlled entry of the needle into the uterus. The track which the needle would take with respect to the ultrasound image was precalibrated and indicated on the ultrasound screen by means of a plastic graticule, marked in centimetres.

Method of transcervical CVS

The method and cannula used have been described previously (Mackenzie *et al.* 1986). An aluminium cannula (Rocket of London) 210 mm long with an outer diameter of 2·3 mm and an inner of 1·3 mm was used in all cases and continuous suction, as in the transabdominal method, was applied.

Cytogenetic analysis

The villi were collected into sodium bicarbonate-buffered RPMI (+5 i.u. heparin per ml) and taken directly to a laboratory where the villi were dissected out into fresh medium. The villus weights were estimated with reference to standards. Tubes containing six samples of villi of known weight were used as a scale against which the weight of the cleaned villi was estimated. There is a direct correlation (Upadyaya *et al.* 1984; Mackenzie *et al* 1986) between villus weights and karyotype success. The cytogenetic details are, therefore, not given in this paper. It is generally accepted that 10 mg of villi is the minimum required for reliable cytogenetic analysis, although 1–5 mg of villi may also allow diagnosis, though unreliably (Upadyaya *et al.* 1984).

Results

The distribution of villus weights obtained by the transcervical and transabdominal methods are given in Table 1. When the two sampling methods were compared with respect to their ability to obtain at least 10 mg of villi a highly significant difference was observed ($\chi^2_M = 13{\cdot}9$, $P<0{\cdot}001$) (McNemar test). Adequate villus samples were obtained by transcervical CVS in 70% of the patients, under these study conditions, but in only 26% of patients by the transabdominal approach. Gestational age was not found to be significantly different between successful and unsuccessful samples for both sampling methods. Table 1 shows the distribution of villus weights obtained from 'anterior' and 'posterior' placentas where 'success' is the proportion of patients in which an adequate sample was obtained. We have applied a broad definition of 'anterior' and 'posterior' in that particularly for the transcervical technique there are only two access routes for sampling. Therefore, fundal placentas were assigned to either the 'anterior'

Table 1. Villus recovery by transabdominal and transcervical chorion villus sampling (CVS)

	Number of patients					
	Transabdominal CVS			Transcervical CVS		
	Posterior placenta	Anterior placenta	Total	Posterior placenta	Anterior placenta	Total
Villus weight (mg)						
0	5	7	12	6	3	9
<5	5	5	10	1	0	1
5–<10	7	8	15	3	2	5
10–<20	7	4	11	5	3	8
20–<30	1	1	2	3	3	6
30–<40	0	0	0	5	8	13
40–<50	0	0	0	2	3	5
50–<60	0	0	0	0	2	2
60	0	0	0	0	1	1
Total no. patients	25	25	50	25	25	50
Approximate mean villus weight (mg)						
SD	6·6	5·4	6·0	15·7	26·5	21·1
	5·6	5·5	5·6	14·1	17·0	16·4
Per cent adequate samples (>10 mg)	32·0	20·0	26·0	60·0	80·0	70·0

or 'posterior' groupings depending on sampling approach. Four fundal placentas were recorded, and of these, three were assigned as 'anterior'. In this study no placenta was localized over the cervical os.

The transabdominal technique obtained an adequate sample in eight posterior placentas and five anterior placentas, compared with the transcervical method, where 20 adequate samples were obtained when the placental site was anterior and 15 when it was posterior. The influence of placental site on the success of these two methods was not significant ($\chi^2 = 1·3$, $P>0·05$).

Discussion

This study was designed to compare the efficacy of two methods of CVS, rather than examining the 'ideal' diagnostic situation, when there are no constraints on time and the optimal gestational age can be chosen for the procedure. This study demonstrates that transabdominal CVS using the technique described is characterized by lower weights of villi recovered than those obtained with the transcervical method. This is in agreement with previous findings (Bovicelli *et al.* 1986; Brambati *et al.* 1986). Brambati *et al.* (1986) employed a larger bore needle, but the weight of villi obtained was still small, indicating that needle size does not seem to affect villus recovery. Before the present study, the operator (W.E.M.) had gained experience with transabdominal CVS in a pilot study involving 40 patients. His experience of transcervical CVS was much greater (over 200). The number of patients in whom villi of any weight was obtained did not differ between the two sampling methods used in this study. Thus the difference in experience of the operator does not appear to be important.

In this study the time taken for sampling (30–60 s) was similar for the two methods. However, in another report on transabdominal CVS (Smidt-Jenson *et al.* 1986) the average time of suction was 240 s (range 80–940 s). If a longer sampling time is a necessary requirement for satisfactory villus recovery by the transabdominal method then it might be expected to be more uncomfortable for the patient, and may, therefore, require some form of analgesia (or local anaesthesia).

It was our expectation that a transabdominal approach would be more successful in obtaining chorionic villi from an 'anterior' placenta than sampling by a transcervical route, but there was no appreciable difference in obtaining access to either an 'anterior' or 'posterior' placenta by either method (Table 1).

A summary of diagnostic series of CVS reported by Laird Jackson, *Chorionic Villus Sampling Newsletter* 1986, shows a spontaneous miscarriage rate following transcervical CVS as being similar to that following transabdominal CVS. If this finding is confirmed then it is difficult to see any advantage for transabdominal CVS, especially for prenatal diagnosis by DNA or biochemical analysis.

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References

Bovicelli, L , Rizzo, N , Montacuti, V & Morandi, R (1986) Transabdominal versus transcervical routes for chorionic villus sampling (Letter). *Lancet* **ii**, 290..

Brambati, B , Simoni, G & Fabro, S. (eds) (1986) In *Chorionic Villus Sampling (Fetal Diagnosis of Genetic Disease in the First Trimester)*. Marcel Dekker, Inc , New York.

Mackenzie, W E , Holmes, D. S , Webb, T , Whitehouse, C & Newton, J. R. (1986) A randomized study of three cannulas for transcervical chorionic villus sampling. *Am J Obstet Gynecol* **154,** 34-39.

Smidt-Jensen, S , Hahnemann, N , Hanr, J., Jensen, P. K A & Therkelsen, A. J. (1986) Transabdominal chorionic villus sampling for first trimester foetal diagnosis: First 26 pregnancies followed to term *Prenat Diagn* **6,** 125-132.

Smidt-Jensen, S. & Hahnemann, N (1984) Transabdominal fine needle biopsy from chorionic villi in the first trimester. *Prenat Diagn* **4,** 163-169

Upadyaya, M., Archer, L M , Harper, P S. *et al* (1984) DNA and enzyme studies on chorionic villi for use in antenatal diagnosis. *Clin Chem Acta* **140,** 39-46

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Measurement of placental alkaline phosphatase in maternal plasma as an indicator of subsequent low birthweight outcome

DAVID J. H. BROCK, LILIAS BARRON

Summary. Placental alkaline phosphatase (P-ALP) was measured by a specific monoclonal antibody-based immunoassay in plasma samples of 117 women who subsequently were delivered of an infant of birthweight less than 2·5 kg. P-ALP values > twice the normal median were found in 32% of maternal plasma samples from low birthweight cases in one series and in 35% in another series, while in normal outcome controls the corresponding value was 8%. The differences were highly significant. The proportion of low birthweight cases with elevated maternal P-ALP values appears to be very similar between 15 and 34 weeks gestation. At 16–18 weeks gestation there is a significant positive correlation ($r = 0{\cdot}40$) between P-ALP and maternal plasma alpha-fetoprotein (AFP) values in low birthweight cases. The use of P-ALP assay in combination with AFP assay appears to improve the detection of pregnancies with subsequent low birthweight outcome.

Infants with low birthweight (defined as <2·5 kg) are associated with an increased risk of neonatal and post-neonatal morbidity and mortality (Drillien 1963; Illingworth 1975). Some years ago it was noted that measurement of maternal serum or plasma alpha-fetoprotein (AFP) between 16 and 20 weeks gestation could identify a proportion of pregnancies with subsequent low birthweight (Brock *et al.* 1977; Wald *et al* 1977). A number of studies have confirmed the association between elevated second trimester maternal AFP and infants of low birthweight (Macri *et al.* 1978; Brock *et al.* 1979; Wald *et al* 1980), both in premature babies and those who were small-for-dates (Brock *et al.* 1980). A prospective study, made throughout pregnancy, showed that the optimal detection of low birthweight by maternal plasma AFP measurement was between 15 and 20 weeks gestation (Brock *et al.* 1982).

Placental alkaline phosphatase (P-ALP) is synthesized in the microvilli of the syncytiotrophoblast and released into the maternal circulation during pregnancy. In the past it has been difficult to distinguish this isoenzyme from the more abundant liver/bone/kidney form which predominates in serum samples The availability of monoclonal antibodies specific for P-ALP, which do not cross-react with the liver/bone/kidney isoenzyme (McLaughlin *et al.* 1983; Travers & Bodmer 1984), makes it possible to devise a sensitive and specific immunoassay (Brock *et al.* 1985) for a potential marker of placental dysfunction. In this study we have examined the value of maternal plasma P-ALP measurement in predicting infants of low birthweight.

Materials and methods

Several years ago we carried out two separate studies on the potential value of maternal

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Human Genetics Unit, University of Edinburgh, Western General Hospital, Edinburgh EH4 2XU
DAVID J H. BROCK
LILIAS BARRON
Correspondence Professor D J Brock

plasma AFP measurement in predicting low birthweight. The first of these (Brock *et al.* 1980) was a case-control study of 226 pregnancies where plasma samples were available between 15 and 20 weeks gestation. The second (Brock *et al.* 1982) was a prospective study on 520 pregnancies where samples were taken at serial intervals between 15 weeks gestation and full term. Plasma samples remaining from the two studies were then stored at −20°C.

In the present investigation all samples with adequate volume remaining from the first study were thawed out and used for P-ALP measurements. The numbers were 71 cases and 75 controls, or 65% of the originals. From the second study there were 1257 samples from 256 pregnancies. Samples were selected from the alphabetical list of patients' names to the letter M, so that about half the originals were assayed. We are not aware of any bias in this selection and there were no differences in the method of storage of the samples.

Samples from women whose pregnancy resulted in the birth of an infant with low birthweight (≤2·5 kg) are referred to as the low birthweight outcome group. All controls had infants with birthweights >2·5 kg. Other details can be found in the earlier reports (Brock *et al.* 1980, 1982).

The immunoassay of P-ALP was carried out using monoclonal antibody H17E2 (Travers & Bodmer 1984) as described previously (Brock *et al.* 1985). Plasma samples were diluted 1:2 in phosphate-buffered saline containing 1% Triton X-100. Maternal plasma AFP was also determined as described previously (Brock *et al.* 1977).

Results

Case-control study

P-ALP values for the 146 samples are shown in Fig. 1. The median activity for the 75 controls was 1·0 u/l; 6 (8%) had activities greater than 2 multiples of the median (MoM). Median activity for the 71 low birthweight cases was 1·4 u/l; 23 (32%) had activities above twice the median value for the controls. The difference between the median values for controls and low birthweight cases was highly significant (median test; $P<0{\cdot}001$). The difference between the proportions in the two groups having values above

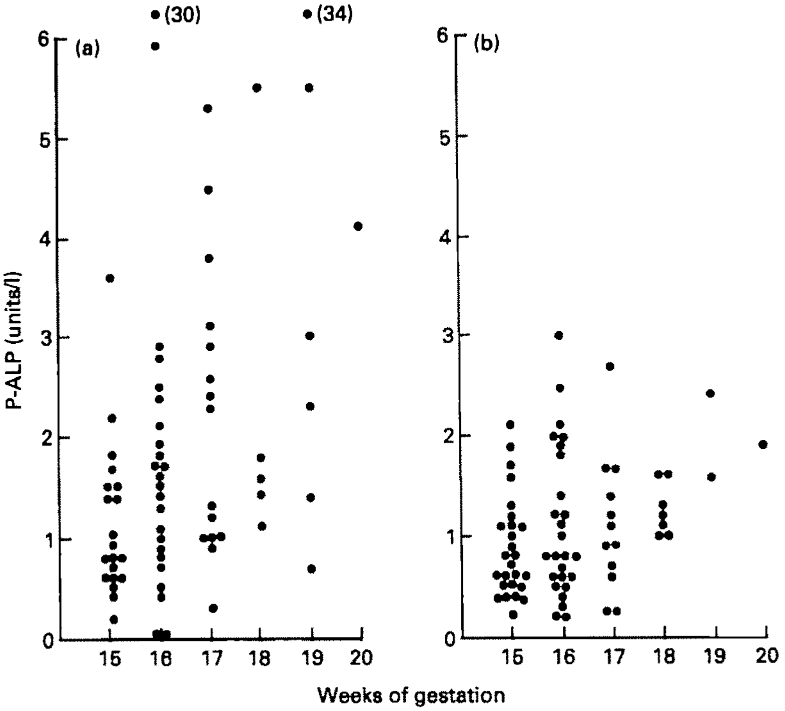

Fig. 1. P-ALP values for low birthweight (a) and normal outcome (b) pregnancies in the case-control study.

Table 1. Plasma placental alkaline phosphatase (P-ALP) values throughout pregnancy for the normal outcome and low birthweight groups

	Normal outcome group			Low-birthweight outcome group		
		P-ALP (units/l)			P-ALP (units/l)	
Gestation (weeks)	No	Median	(Range)	No.	Median	(Range)
15	17	0·9	(0·5–1·6)	3	1·1	(1·0–2·1)
16	82	1·0	(0·3–3·5)	28	1·1	(0·4–2·6)
17	36	1·0	(0·5–2·8)	15	1·3	(0·7–4·2)
18	34	0·9	(0·3–2·9)	14	2·1	(0·6–4·6)
19	30	1·4	(0·6–10·7)	8	2·6	(1·2–4·6)
20	60	1·5	(0·1–6·2)	12	2·1	(1·0–3·9)
21	27	1·6	(0·4–3·9)	18	2·2	(1·0–4·3)
22	25	1·4	(0·7–10·8)	4	3·2	(2·1–4·1)
23	32	2·1	(0·3–6·0)	7	2·8	(1·2–4·9)
24	52	2·3	(0·8–5·5)	10	4·6	(2·2–8·6)
25	29	2·5	(1·1–11·2)	17	4·5	(0·6–21·8)
26	31	2·9	(1·1–26·0)	8	6·3	(4·5–19·4)
27	30	4·9	(1·6–14·8)	8	5·7	(1·9–37·6)
28	56	4·9	(1·3–18·2)	10	7·2	(4·5–17·9)
29	31	4·3	(2·1–17·3)	12	5·5	(2·4–51·7)
30	29	6·5	(3·0–25·5)	9	17·3	(6·2–224)
31	49	8·7	(2·6–21·4)	12	11·0	(5·0–39·5)
32	60	9·0	(2·1–41·7)	11	11·5	(4·7–259)
33	55	12·4	(0·7–40·2)	12	18·6	(3·0–69·8)
34	58	12·0	(0·2–33·3)	11	13·2	(3·2–33·0)
35	55	14·7	(5·5–37·9)	9	29·9	(3·6–69·5)
36	55	17·3	(8·4–38·7)	8	15·3	(1·8–355)
37	29	16·8	(6·5–32·9)	1	16·0	
38	29	18·0	(0·9–35·3)			
39	13	23·4	(0·3–38·2)			
40	6	14·0	(8·9–34·2)			
15–40	1010			247		

twice the normal median was also highly significant (χ^2 test; $P<0{\cdot}001$).

Prospective study (whole series)

The normal range for P-ALP between 15 and 40 weeks gestation was constructed from 1010 samples taken from 216 pregnancies. The median number of samples per woman was 7. The median and range of value for each week of gestation is shown in Table 1. Activities rose progressively with advancing gestation with an increasing scatter of values.

P-ALP activities were determined on 247 samples from 46 women with low birthweight outcome. The median number of samples per woman was 6. Median values for the low birthweight group are also shown in Table 1.

The number and proportion of P-ALP activities greater than the normal median and greater than twice the normal median for both normal and low birthweight cohorts are shown in Table 2. Samples were grouped into 5-week periods. The differences between the proportions of normal outcome and low birthweight outcome pregnancies with values greater than 2 MoM were significant for each 5-week grouping and for the whole series (χ^2 test; $P<0{\cdot}001$).

Comparison between P-ALP and AFP data

The first sample from each woman in the prospective series, between 16 and 18 weeks gestation, was used for AFP screening. There were 116 samples from the normal outcome group and 41 samples from the low birthweight group.

In the normal outcome group the median value for P-ALP was 1·0 u/l, and 6 (5·6%) women had values above 2 MoM In the low

Table 2. Numbers (and proportions) of normal and low birthweight outcome groups with plasma P-ALP values above the median and twice median

	No. (%) ⩾ normal median		No. (%) ⩾ twice normal median	
Gestational weeks	Normal	Low birthweight	Normal	Low birthweight
15–19	106/199 (53)	53/68 (80)	19/199 (9·5)	24/68 (35)
20–24	103/196 (53)	42/51 (82)	18/196 (9·2)	19/51 (37)
25–29	89/177 (50)	42/55 (76)	22/177 (12·4)	21/55 (38)
30–34	124/251 (49)	35/55 (64)	15/251 (6·0)	19/55 (35)
35–40	85/187 (45)	9/18 (50)	6/187 (3·2)	4/18 (22)
15–40	507/1010 (50)	181/247 (73)	80/1010 (7·9)	87/247 (35)

Table 3. Plasma placental alkaline phosphatase (P-ALP) values for first samples only in normal and low birthweight outcome groups (prospective series, 16–18 weeks)

		P-ALP (units/l)		
	No.	Median	(Range)	No. (%) > twice normal median
Normal outcome	116	1·0	(0·3–3·5)	6 (5·2)
Low birthweight	41	1·2	(0·4–3·6)	10 (24)

Table 4. Comparison of AFP and P-ALP data in 16–18 week samples

	Normal outcome	Low birthweight outcome
AFP only > 2 MoM	6	6
P-ALP only > 2 MoM	6	4
Both AFP and P-ALP > 2 MoM	0	6
Neither AFP nor P-ALP > 2 MoM	104	25
Total	116	41

birthweight group the median value for P-ALP was 1·2 u/l, while 10 (24%) women had values above twice the normal median (Table 3). The difference between medians was significant (median test; $P<0{\cdot}01$) as well as the difference between proportions of the two groups with values above twice the normal median (χ^2 test; $P<0{\cdot}05$).

There was no significant correlation between P-ALP and AFP data in the 116 samples with normal outcome, but in the 41 low birthweight outcome samples the correlation coefficient was 0·40 ($P<0{\cdot}01$; d.f. 39).

Table 4 shows the distribution of raised AFP and P-ALP values for both normal outcome and low birthweight cohorts for samples taken at 16–18 weeks gestation.

Discussion

The use of an immunoassay based on a monoclonal antibody (H17E2) with specificity for the placental isoenzyme of alkaline phosphatase (Travers & Bodmer 1984) removes the inaccuracies of previous assays where a lesser degree of specificity could be achieved by heat inactivation, by differential inhibition or by cross-absorbed polyclonal antisera. Similar assays, though using different monoclonal antibodies against P-ALP, have been reported by

McLaughlin *et al.* (1983) and by Contractor *et al.* (1985). Although both these groups examined a range of pregnancy sera, no obvious clinical value in P-ALP immunoassays emerged.

The data presented here suggest that measurement of maternal P-ALP may have a role in the early detection of pregnancies with low birthweight outcome. We examined two different cohorts of women; one selected case-control group (Brock *et al.* 1980) and the other a group which had been assembled prospectively (Brock *et al.* 1982). When P-ALP was examined throughout pregnancy, very similar proportions of the low birthweight group had elevated levels at different gestational stages (Table 2). Amongst the low birthweight group 87 of 247 samples had P-ALP values above twice the normal median, while among the normal group there were 80 raised P-ALP values in 1010 samples. This gives an overall relative risk of 4·4. In contrast, AFP data on the same set of samples (Brock *et al.* 1982) showed that elevated values in the low birthweight group occurred mainly in the early gestational weeks.

In the case-control cohort (Fig. 1), 23 of 71 low birthweight samples had raised P-ALP values, against 6 of 75 normals. This gives a relative risk of 4·0. When the 16 to 18 weeks subgroup of the prospective series was examined (Table 3), the relative risk was 4·7. Thus, relative risk figures for two separate cohorts of patients are comparatively constant.

There was a significant positive correlation between P-ALP and AFP data in the low birthweight group for samples taken between 16 and 18 weeks gestation. Relative risks for elevated AFP alone (4·7) and elevated P-ALP alone (3·8) were similar (Table 4). However, it is noteworthy that simultaneously elevated AFP and P-ALP occurred only amongst the low birthweight samples. Thus the use of P-ALP assay in combination with AFP screening contributes to the detection of low birthweight outcomes

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References

Brock, D J. H., Barron, L , Jelen, P , Watt, M & Scrimgeour, J. B. (1977) Maternal serum alphafetoprotein measurements as an early indicator of low birth-weight *Lancet* **ii**, 267-268.

Brock, D J. H , Barron, L., Duncan, P., Scrimgeour, J. B. & Watt, M. (1979) Significance of elevated mid-trimester maternal plasma alphafetoprotein values *Lancet* **i**, 1281-1282.

Brock, D J. H , Barron, L. & Raab, G. M. (1980) The potential of mid-trimester alphafetoprotein measurement in predicting infants of low birthweight *Br J Obstet Gynaecol* **87**, 582-585

Brock, D. J H., Barron, L., Watt, M , Scrimgeour, J B. & Keay, A. J. (1982) Maternal plasma α-fetoprotein and low birthweight a prospective study throughout pregnancy. *Br J Obstet Gynaecol* **89**, 348-351

Brock, D. J. H., Bedgood, D., Barron, L. & Hayward, C (1985) Prospective prenatal diagnosis of cystic fibrosis. *Lancet* **i**, 1175-1178

Contractor, S. F , Holmes-Ievers, E , Morgan, A , Oakey, M. & Staines, N A (1985) A monoclonal antibody based solid-phase enzyme binding assay to measure levels of placental alkaline phosphatase in serum of women during pregnancy. *J Immunol Methods* **79**, 99-108.

Drillien, C. M (1963) *The Growth and Development of Prematurely Born Infants* Churchill Livingstone, Edinburgh.

Illingworth, R S. (1975) *The Development of the Infant and Young Child: Normal and Abnormal*, 6th edn, Churchill Livingstone, Edinburgh.

McLaughlin, P. J , Gee, H. & Johnson, P. M. (1983) Placental-type alkaline phosphatase in pregnancy and malignancy plasma. specific estimation using a monoclonal antibody in a solid phase enzyme immunoassay. *Clin Chim Acta* **130**, 199-209

Macri, J N , Weiss, R R , Libster, B. & Cagan, M. A. (1978) Maternal serum AFP and low birthweight. *Lancet* **ii**, 660

Travers, P. & Bodmer, W F (1984) Preparation and characterisation of monoclonal antibodies against placental alkaline phosphatase and other human trophoblast-associated determinants *Int J Cancer* **33**, 633-641.

Wald, N., Cuckle, H., Stirrat, G M , Bennett, M J. & Turnbull, A C (1977) Maternal serum-alphafetoprotein and low birth-weight. *Lancet* **ii**, 268-269.

Wald, N , Cuckle, H S., Boreham, J. & Turnbull, A. C (1980) Maternal serum alphafetoprotein and birthweight. *Br J Obstet Gynaecol* **87**, 860-863

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Gestational diabetes and impaired glucose tolerance of pregnancy in Riyadh

T. Al-SHAWAF, A. AKIEL, S. A. S. MOGHRABY

Summary. A total of 1088 pregnant women was screened for abnormalities in glucose metabolism at the initial antenatal visit; those with specific risk factors were screened again after 28 weeks gestation. In 210 (19·3%) plasma glucose measured 2 h after a 75 g glucose load was ≥7·8 mmol/l (140 mg/dl). Follow-up glucose tolerance tests revealed an overall prevalence of abnormal tests of 10·3% (112 of 1088) according to the WHO criteria, of which 21 (1·9%) were diagnosed as gestational diabetes, and 91 (8·4%) as impaired glucose tolerance. This high prevalence was significantly related to age, parity and body mass index. Screening and diagnosis using criteria set by the WHO were found acceptable and are recommended to help resolve the international disagreement on diagnostic criteria of glucose metabolism abnormalities in pregnancy.

The World Health Organization (WHO) Study Group Report (1985) and the Second International Workshop Conference on Gestational Diabetes Mellitus (SIW-CGD) (1985) advised that pregnant women be considered a target population for screening programmes to detect abnormality in carbohydrate metabolism. Even minor abnormalities in carbohydrate metabolism may influence the pregnancy adversely (Beard & Hoet 1982; Freinkel 1981). The prevalence differs in various parts of the world, partly due to the use of different screening and diagnostic criteria (Hadden 1985). The criteria for diabetes mellitus and impaired glucose tolerance reported by the WHO Study Group (1985) are now universally accepted in the general population, but not in pregnancy (SIW-CGD 1985), although the WHO recommended its use in pregnant women. Several criteria based on an oral glucose tolerance test (GTT) are now used for diagnosis (Table 1).

Similar disagreement seems to exist with screening programmes The measurement of plasma glucose 1 h after a 50 g oral glucose load (O'Sullivan *et al.* 1973) has been recommended by the SIW-CGD (1985), but this test may overestimate the number requiring a diagnostic GTT (unpublished data). The use of a random plasma glucose measurement (Lind & Anderson 1984) requires knowledge of the time interval from the last meal which may be difficult to assess accurately in some populations. Plasma glucose measurement 2 h after a 75 g glucose load is suggested as a screening programme by the WHO and has been found to be more efficient than the 1-h test (Merkatz *et al.* 1980)

SIW-CGD (1985) suggested that the 75 g oral glucose dose could eventually replace the 100 g and 50 g glucose loads. We report our experience with a screening and diagnostic programme on unselected consecutive pregnant women, as recommended by WHO (1985).

The Department of Obstetrics and Gynaecology, Medical College, King Saud University, Riyadh, Saudi Arabia
T. AL-SHAWAF *Assistant Professor*
A AKIEL *Assistant Professor*
S A. S. MOGHRABY *Assistant Professor*

Correspondence: Dr T Al-Shawaf, Department of Obstetrics and Gynaecology, King Abdul Aziz University Hospital, Medical College, King Saud University, PO Box 245, Riyadh 11411, Saudi Arabia

Table 1. Plasma glucose values diagnostic for diabetes mellitus (gestational diabetes) according to different oral glucose tolerance tests (GTT)*

GTT*	Glucose load (g)	Plasma glucose (mmol/l)			
		Fasting	1 h	2 h	3 h
WHO (1985)	75	>7·8	—	>11	—
SIW-CGD (1985)	100	>5·8	>10·6	>9·2	>8·1
Modified O'Sullivan†	75	>5·8	>10·3	>7·8	>6 8
Oxford‡	75	>5·8	>12·5	>9·5	>7·5

* The WHO criteria require at least one critical value for diagnosis (a 2-h value of 7·8–11 mmol/l indicates impaired glucose tolerance), for the other three methods at least two critical values are required

† Abell & Beischer (1975).

‡ M D G. Gillmer (personal communication).

Subjects and methods

During a 12-month period, pregnant women attending our antenatal clinic at the King Abdul Aziz University Hospital (King Saud University Medical College, Riyadh, Saudi Arabia) who were not known to be diabetic before the onset of pregnancy were screened for abnormal carbohydrate metabolism. The 1088 consecutive pregnant women who were included in the study were all of Arab origin (55% Saudis and 45% of other Arab nationalities).

At their first visit to the antenatal clinic the women were informed about the screening programme and they agreed to participate. The test was performed the week after the first visit irrespective of gestational age. Fasting was not required on the day of screening, although in fact over 90% of the women came fasting. They were given a solution of 75 g glucose to drink over 5 min. Venous blood was sampled 2 h after the glucose load, during which time they had no food or drink. The results were reviewed at the next antenatal visits. If the plasma glucose value was ≥7·8 mmol/l (140 mg/dl), a GTT was requested and the woman was instructed to continue on her unrestricted usual diet. The GTT was performed in the morning, after an overnight fast of between 10 and 12 h. Venous plasma glucose was measured fasting and then at 1, 2 and 3 h after a 75 g oral glucose load. Diagnosis of gestational diabetes (or glucose intolerance) was made according to the WHO criteria and the results were compared with the other criteria listed in Table 1.

Women who were screened before 26 completed weeks gestation and had strong clinical or reported risk factors for gestational diabetes (previous unexplained stillbirth, a close family member with diabetes, previous large baby, obesity, grand multiparity, fetus suspected of being large-for-gestational-age) were requested to repeat the single 2-h test between 28 and 32 weeks gestation. In addition, the women who had an abnormal glucose screening-value (>7·8 mmol/l), but a normal GTT, were required to have a repeat single 2-h test.

Special attention was given to the effect of age and parity on the development of impaired glucose tolerance. Data on body mass index (BMI) [weight/height^2 (kg/m^2)] were collected at the initial antenatal visit, and at the last week before delivery. Two groups were identified according to gestational age at the first visit when the weight was recorded; one group included those recorded at 13 weeks or earlier and the other group those after 13 weeks gestation. This was to overcome the lack of information on pre-pregnancy weight. Women with a BMI of more than 24 (>120% ideal body weight) were considered overweight.

Women diagnosed as having gestational diabetes or impaired glucose tolerance were followed in the high risk obstetric/diabetic clinic while those with normal glucose metabolism received routine prenatal care.

Biochemical methods

Plasma was separated immediately and plasma glucose was measured by a hexokinase method using an auto analyser. The coefficient of variation for glucose estimation in our laboratory for the low and high target values is 3% and 4% respectively.

Table 2. Plasma glucose screening values by gestational age

	Plasma glucose (mmol/l) at			
	<26 weeks	>26 weeks	t^*	P
Normal screening-values	5·8 (1·0)	5·9 (1·0)	2·89	<0·01
Normal screen+normal GTT	5·9 (1·2)	6·2 (1·2)	3·97	<0·001
Normal screen+normal GTT+abnormal GTT	6·2 (1·6)	6·4 (1·7)	3·06	<0·01

Results are mean (SD) values.

* Paired t-test

Statistical analysis

Analysis of data used Student's paired t-test, the χ^2-test and Yates' correction and the Mann–Whitney U-test.

Results

A total of 1088 women had a single 2-h test as a screening procedure. After a 75 g oral glucose load, the mean 2-h screening plasma glucose value was significantly higher in the women tested after 26 weeks gestation than when tested before 26 weeks (Table 2).

The prevalence of abnormal glucose screening-values and abnormal GTT by the WHO criteria is shown in Table 3. Initial screening after 26 weeks gestation identified more abnormal GTT than screening before 26 weeks (χ^2 = 9·37, P<0·01). The repeat 2-h screening tests between 28 and 32 weeks gestation also identified more abnormal GTT than the initial screening tests before 26 weeks, but this difference was not significant (χ^2 = 3·04, P>0·05). However, the prevalence of abnormal GTT was not significantly different between the women who were screened initially after 26 weeks and those rescreened between 28 and 32 weeks because of risk factors (χ^2 = 0·06, P>0·1). The prevalence of abnormal screening-values followed a similar pattern to the prevalence of abnormal GTT, in the different groups. There were 124 (20·7%) Saudi women with abnormal screening-values and 72 (12%) with abnormal GTT; in non-Saudi Arab women the corresponding numbers were 81 (16·6%) and 40 (8·1%) respectively. The differences between the two ethnic groups were not statistically significant (for abnormal screening values: χ^2 = 2·65, P>0·05; for abnormal GTT: χ^2 = 3·7, P>0·05).

Table 3. Prevalence of abnormal screening-values and abnormal GTT results (number and %)

	n	%
Patient screened at initial antenatal visit		
<26 weeks gestation	715	100
Abnormal screening-values	84	11·8
Abnormal GTT	45	6 3
>26 weeks gestation	373	100
Abnormal screening-values	70	18·8
Abnormal GTT	39	10·5
Patient rescreened at 28–32 weeks	302 (of 715)	100
Abnormal screening-values	56	18·5
Abnormal GTT	28	9·3
Total population screened	1088	100
Abnormal screening-values	210*	19·3
Abnormal GTT	112	10·3

* Twenty-four women had no GTT because of refusal or delivery before the test was done

In 21 women the GTT results were consistent with diabetes mellitus (gestational diabetes mellitus) on the 2-h plasma glucose value (five of them had fasting plasma glucose values of >7·8 mmol/l). Table 4 shows the prevalence of impaired glucose tolerance according to the different diagnostic criteria. On subclassification by the fasting plasma glucose level at the time of diagnosis according to Freinkel *et al.* (1985), 80 (71%) were class A1 (<5·8 mmol glucose/l), 27 (24%) were class A2 (5·8–<7·2 mmol/l) and 5 (4·5%) were class B1 (>7·2 mmol/l).

Tables 5 and 6 describe the maternal characteristics. Women with an abnormal GTT were on average older and heavier than women with normal screening-values or those with abnormal screening-values but a normal GTT. There was no statistical difference in age or BMI between women with normal screening-values and those with abnormal screening-values but a normal GTT; 90% of the women with an abnormal GTT had a BMI of >24 at the initial antenatal visit,

Table 4. Prevalence of abnormal glucose tolerance tests by different criteria* (number and % of total women screened)

GTT	Impaired glucose tolerance (gestational impaired glucose tolerance)	Diabetes mellitus (gestational diabetes)
WHO (1985)	91 (8·4%)	21 (1·9%)
SIW-CGD (1985)		45 (4·1%)
Modified O'Sullivan	58 (5·3%)	21 (1·9%)
Oxford		29 (2·7%)

* See Table 1

whether this was before or after 13 weeks gestation. As age advanced (by yearly or 5-year increments) and as parity increased (by single parity or by parity groups) there was a progressive increase in the prevalence of abnormal GTT.

There was no difference between the infants born in the different groups, in terms of sex distribution, or rate of low Apgar scores (<6) at 1 or 5 min (Table 7). However, the women with an abnormal GTT gave birth to slightly heavier infants compared with those who had normal screening-values and also those who had abnormal screening-values but a normal GTT. Significantly more large infants (>4 kg) were born in the group with abnormal GTT. There were 20 infants with congenital abnormalities born in the group with normal screening-values compared with two in the group with abnormal GTT (χ^2 = 0·00089, *P*>0·5).

Discussion

There is an increasing need for well-defined and uniformly accepted criteria to diagnose abnormality in glucose metabolism in pregnancy We selected the WHO criteria to provide uniform and consistent diagnostic values before, during and after pregnancy (Lind 1984). This is especially important in developing countries where easy and uniform criteria could be recognized by a large number of health providers There was general acceptance of the screening test, although some women found the glucose solution unpalatable; they did not seem to mind waiting for 2 h for the screening test to finish.

The mean+2SD glucose screening values in normal subjects corresponds to the upper limit of normality in the WHO criteria. In our study the 2-h plasma glucose values were significantly higher in women screened after 26 weeks gestation and more of them had abnormal screening-values and an abnormal GTT. Our results agree with those of Jovanovic & Peterson (1985) who found the highest proportion of abnormal GTT results in the third trimester but differ from those of Lavin *et al* (1981) who reported a similar prevalence of abnormal GTT before and after 26 weeks gestation. Our findings that the prevalence of abnormal GTT was no higher in women with risk factors for diabetes than in

Table 5. Maternal characteristics

	Patient group				
	Normal screening-values	Abnormal screening-values		Significance of differences (*P*)*	
Variable	(*n* = 884)	Normal GTT (*n* = 93)	Abnormal GTT (*n* = 112)	Abnormal GTT *vs* normal screen	Abnormal GTT *vs* normal GTT
Gestation at first visit (weeks)	17·1 (8·9)	17·9 (9·9)	18·8 (9·1)	>0·5	>0·5
Age (years)	25·2 (5·1)	27 (5·1)	29·4 (6·0)	<0·001	<0·01
Height (cm)	156 (6)	155 (6)	154 (6)	<0·01	>0·1
Body mass index (kg/m²)					
At first visit					
≤13 weeks	25·9 (4·9)	26·1 (5·1)	28·8 (5·0)	<0·01	<0·01
>13 weeks	27·6 (5·1)	27·8 (4·6)	31·1 (4·9)	<0·001	<0·001
At last visit	30 (4·8)	29·6 (5·0)	31·4 (4·6)	<0·001	<0·01

Results are mean (SD) values

* Two-sample *t*-test.

Table 6. Distribution by age, parity and weight

	Patient group		
		Abnormal screening-values	
Variable	Normal screening-values ($n = 884$)	Normal GTT ($n = 93$)	Abnormal GTT ($n = 112$)
5-year age groups[a]			
15–19	104	4	4
20–24	329	26	20
25–29	266	33	31
30–34	129	18	31
25–39	49	12	20
>40	7	—	6
Parity[b]			
0	221	22	14
1–4	569	53	60
5–9	92	17	35
>10	2	1	3
Body mass index			
>24 (kg/m^2)[c]			
At first visit			
≤13 weeks	249***	30*	48
>13 weeks	304***	35**	53
At last visit	777*	80*	108

[a] Significance by Mann-Whitney U two-tailed test Z value = 5·83, $P<0{\cdot}001$.

[b] Significance by Mann-Whitney U two-tailed test Z value = 7 12, $P<0{\cdot}001$

[c] Significance by χ^2 with Yates' correction for obesity; normal screen *vs* abnormal GTT and normal GTT *vs* abnormal GTT. *$P<0{\cdot}02$, **$P<0{\cdot}05$; ***$P<0{\cdot}001$

those without such risk factors are supported by previous reports (O'Sullivan *et al.* 1973; Lavin *et al.* 1981).

In our series 21 (1·9%) women had an abnormal GTT consistent with gestational diabetes mellitus by the WHO criteria; a higher prevalence than reported by others using similar diagnostic criteria (Pettitt *et al.* 1985; Lind & Anderson 1984). Impaired glucose tolerance was diagnosed in 91 (8·4%), a lower prevalence than the 10% reported by Pettitt *et al.* (1985). Our overall prevalence of 10·3% was higher than that reported from other centres (Merkatz *et al.* 1980; Lind & Anderson 1984). The prevalence of abnormal GTT was 7·3% in women under 33 years of age and 7·8% in those of parity 2 or less. Of the women who had a BMI of <24 at their initial visit before 14 weeks only 3% had an abnormal GTT. Other workers, using the SIW-CGD (1985) criteria, have reported prevalences of abnormal GTT between 1·6 and 12·3% (O'Sullivan *et al.* 1973; Freinkel *et al.* 1985; Lavin *et al.* 1981; Amankwah *et al.* 1977, Mestman 1980), and Gillmer *et al* (1980), using the area under the GTT curve, reported a 1·5% prevalence. Analysis of the GTT results (Table 4) illustrates the difficulty in comparing data when different sets of diagnostic criteria are used. H. H. Fatani (1986 unpublished observations) estimated the prevalence of diabetes mellitus to be 4·5% in 17 000 of the general population of Saudi Arabia and 80·8% of diabetics studied in a Riyadh general hospital were non-insulin-dependent (A. A. Hagroo *et al.* 1986, unpublished observations). This may imply a high incidence of impaired glucose tolerance in our general population, and is reflected in the high prevalence of this condition in the pregnant women in this study.

Analysis of the fasting plasma glucose level (Freinkel *et al.* 1985), and modified from White's

Table 7. Characteristics of the newborn infant

	Patient group		
		Abnormal screening-values	
Variable	Normal screening-values ($n = 884$)	Normal GTT	Abnormal GTT
Sex			
Male	430 NS	51 NS	59
Female	458 NS	43 NS	53
Low Apgar scores (<6)			
At 1 min	144 NS	14 NS	22
At 5 min	14 NS	4 NS	1
Birthweight (kg)			
Mean	3·32***	3·37**	3·50
(SD)	(0·44)	(0·45)	(0·48)
Birthweight >4 kg			
n (%)	69 (8)***	11 (12) NS	18 (16)

Significance of difference between normal screen and abnormal GTT groups: NS, $P>0{\cdot}1$, ***$P<0{\cdot}001$.
Significance of difference between normal GTT and abnormal GTT groups: NS, $P>0{\cdot}05$, **$P<0{\cdot}05$
Tests of significance. two-sample t-test for birthweight, χ^2 for sex, low Apgar score, >4 kg birthweight and sex distribution between the groups.

classification of diabetes in pregnancy, showed that the majority of women (71%) were class A1. Recent reports have suggested that women with class A2 and B1 express a more severe form of gestational diabetes during pregnancy and they are more likely to have persistence of diabetes or impaired glucose tolerance after pregnancy (Freinkel *et al.* 1985; Metzger *et al.* 1985).

Analysis of selected maternal and neonatal characteristics identified several related features. Increasing age was significantly associated with increased prevalence of abnormality in GTT ($P<0{\cdot}001$), women with an abnormal GTT were on average 4·2 years older than the others. Increasing parity was also highly associated with abnormal GTT ($P<0{\cdot}001$). Women with abnormal GTT were heavier and more of them were overweight.

These findings are similar to previous reports (O'Sullivan *et al.* 1973; Freinkel *et al.* 1985; Mestman 1980; Gillmer *et al.* 1980; Metzger *et al.* 1985; Sepe *et al.* 1985).

Infants born to women with an abnormal GTT were on average heavier than those born in the normal group ($P<0{\cdot}001$), which is consistent with other reports (Jovanovic & Peterson 1985; Gillmer *et al.* 1980; Widness *et al.* 1985). But in contrast to Widness *et al.* (1985) we found significantly more heavy infants (>4 kg) born to women with an abnormal GTT and no difference in sex distribution in the offspring. Infants born to women with gestational diabetes do not show an increased rate of congenital abnormalities (Beard & Lowy 1982; Sepe *et al.* 1985) as we also noticed.

The use of internationally agreed criteria to diagnose abnormalities in glucose metabolism in pregnancy is possible (Hadden 1985), and the WHO criteria have been recommended (Lind 1984; Lind & Anderson 1984). In our series the diagnosis of gestational diabetes was comparatively unaffected by the use of different sets of criteria. The National Diabetes Data Group (1979) suggested that in pregnancy a plasma glucose level of between 6·7 mmol/l (120 mg/dl) and 9·1 mmol/l (164 mg/dl) 2 h after an oral glucose load deserved greater attention and this has been confirmed recently (Tallarigo *et al.* 1986). Increased birthweight, fat stores, muscle mass and heightened insulin secretion may be present in the infants of mothers with even the mildest gestational diabetes (Ogata *et al.* 1980) These arguments support the inclusion of impaired glucose tolerance in pregnancy as another condition requiring control (Pettitt *et al.* 1985). Classification of patients according to Freinkel *et al.* (1985) using fasting plasma glucose levels will enable the severity and management to be assessed further. Obstetricians and physicians then must agree on the most convenient and economical method of screening for abnormalities in glucose metabolism (Editorial, 1985), influenced by their local circumstances. Lind (1984) advised the use of a random blood glucose level for screening but the 2-h plasma glucose estimation after a 75 g load is more convenient because fewer women would require a GTT (T. Al-Shawaf *et al.*, unpublished observations; Merkatz *et al.* 1980).

In Saudi Arabia, a developing affluent society with continuing improvement in health and social circumstances, a programme for the detection of abnormalities in glucose metabolism in pregnancy is important, particularly since many women are of high parity, older and overweight. We would advise the use of the WHO criteria for their GTT plasma glucose values estimated fasting and 2 h after a 75 g glucose load. Long-term follow-up after pregnancy is required to assess the consequence of the spectrum of impaired glucose tolerance in the mother and her children.

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References

Abell, D. A & Beischer, N. A. (1975) Evaluation of the three hour oral glucose tolerance test in detection of significant hyperglycemia and hypoglycemia in pregnancy. *Diabetes* **24**, 874-880

Amankwah, K S.; Prentice, R. L & Fleury, F J (1977) The incidence of gestational diabetes *Obstet Gynecol* **49**, 497-498.

Beard, R W & Hoet, J J. (1982) Is gestational diabetes a clinical entity. *Diabetologia* **23**, 307-312.

Beard, R. W. & Lowy, C (1982) The British survey of diabetic pregnancies. *Br J Obstet Gynaecol* **89**, 783-786

Editorial (1985) Diabetes in pregnancy. *Lancet* **i**, 961-962

Freinkel, N. (1981) Pregnant thoughts about metabolic control and diabetes. *N Engl J Med* **304**, 1357-1359

Freinkel, N., Metzger, B E , Phelps, R. L., Dooley, S. L , Ogata, E S., Radvany, R. M & Beltran, A (1985) Heterogeneity of maternal age, weight, insulin secretion, HLA antigens, and islet cells antibodies and the impact of maternal metabolism on pancreatic B-cell and somatic development in the offspring. *Diabetes* **34 (Suppl. 2)**, 1-7

Gillmer, M D. G , Oakley, N W , Beard, R W , Nithyanathan, R & Cawston, M. (1980) Screening for diabetes during pregnancy. *Br J Obstet Gynaecol* **87**, 377-382

Hadden, D. R (1985) Geographic, ethnic and racial variations in the incidence of gestational diabetes mellitus *Diabetes* **34 (Suppl. 2)**, 8-12

Jovanovic, L & Peterson, C. M (1985) Screening for gestational diabetes. Optimum timing and criteria for retesting *Diabetes* **34 (Suppl. 2)**, 21-23

Lavin, J. P , Barden, T. P. & Miodovnik, M (1981) Clinical experience with a screening program for gestational diabetes. *Am J Obstet Gynecol* **141**, 491-494.

Lind, T (1984) Antenatal screening for diabetes mellitus. *Br J Obstet Gynaecol* **91**, 833-834.

Lind, T , & Anderson, J (1984) Does random blood glucose sampling outdate testing for glycosuria in the detection of diabetes during pregnancy? *Br Med J* **289**, 1569-1571.

Merkatz, I R , Duchon, M A , Yamashita, T. S. & Houser, H. B. (1980) A pilot community-based screening program for gestational diabetes *Diabetes Care* **3**, 453-457

Mestman, J H. (1980) Outcome of diabetes screening in pregnancy and perinatal morbidity in infants of mothers with mild impairment in glucose tolerance. *Diabetes Care* **3**, 447-452.

Metzger, B. E , Bybee, D. E., Freinkel, N., Phelps, R L , Radvany, R. M & Vaisrub, N (1985) Gestational diabetes mellitus. Correlation between phenotypic and genotypic characteristics of the mother and abnormal glucose tolerance during first year postpartum *Diabetes* **34 (Suppl. 2)**, 111-115.

National Diabetes Data Group (1979) Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes* **28**, 1039-1057

Ogata, E. S , Freinkel, N , Metzger, B. E , Phelps, R. L., Depp, R , Boehm, J J. & Dooley, S. (1980) Perinatal islet function in gestational diabetes: assessment by cord plasma C-peptide and amniotic fluid insulin *Diabetes Care* **3**, 425-429.

O'Sullivan, J. B., Mahan, C. M , Charles, D & Dandrow, R V. (1973) Screening criteria for high-risk gestational diabetic patients. *Am J Obstet Gynecol* **116**, 895-900

Pettitt, D J , Bennett, P H , Knowler, W E , Baird, H. R. & Aleek, K A (1985) Gestational diabetes mellitus and impaired glucose tolerance during pregnancy Long-term effects on obesity and glucose tolerance in the offspring. *Diabetes* **34 (Suppl. 2)**, 119-122

Second International Workshop-Conference on Gestational Diabetes Mellitus (SIW-CGD) (1985) Summary and recommendations. *Diabetes* **34 (Suppl. 2)**, 123-126

Sepe, S. J , Connell, F A., Geiss, L. S. & Teutsch, B. M. (1985) Gestational diabetes incidence, maternal characteristics, and perinatal outcome *Diabetes* **34 (Suppl. 2)**, 13-16.

Tallarigo, L., Giampietro, O , Penno, G , Miccoli, R., Gregori, G & Navalesi, R. (1986) Relation of glucose tolerance to complications of pregnancy in non-diabetic women. *N Engl J Med* **315**, 989-992.

Widness, J A., Cowett, R. M., Couston, D R , Carpenter, M W. & Oh, W. (1985) Neonatal morbidities in infants of mothers with glucose intolerance in pregnancy *Diabetes* **34 (Suppl. 2)**, 61-65

World Health Organization Study Group Report (1985) *Diabetes mellitus,* Technical Report series 727, 9-20 WHO, Geneva

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Obesity and urinary incontinence in women

P. L. DWYER, E. T. C. LEE, D. M. HAY

Summary. In a series of 368 incontinent women who presented to our urodynamic clinic for assessment, 232 (63%) were diagnosed as having genuine stress incontinence, and 136 (27%) as having detrusor instability. Obesity (>20% more than average weight for height and age) was significantly more common in women with genuine stress incontinence and detrusor instability than in the normal population. In those with detrusor instability the body mass index was found to increase with age and parity. In women with genuine stress incontinence the body mass index increased with age and the number of previous incontinence operations; it was higher in nulliparous than in parous women. There was no significant difference between obese and non-obese women in any of the urodynamic variables measured in the two incontinence groups.

Obesity is commonly encountered in women with urinary incontinence and is thought to be an important consideration in its pathophysiology. As there is little evidence to support this clinical impression, a prospective study using urodynamic measurements was initiated in a group of incontinent women in order to obtain reliable height and weight data in a series of incontinent women diagnosed as having genuine stress incontinence and detrusor instability. The prevalence and significance of obesity in these patients was investigated by comparing the data with standard height and weight statistics from a similar population. The relation between weight and other possible aetiological factors such as age, parity and previous incontinence surgery was assessed, and cystometry and uroflowmetry measurements were compared in obese and non-obese incontinent women. The data were analysed for statistically significant differences between the two groups for any of the measured variables.

Department of Gynaecology, Princess Royal Hospital, Salthouse Road, Hull
P L. DWYER
E. T C. LEE
D. M. HAY

Correspondence: P L. Dwyer, 71 Collins Street, Melbourne 3000, Australia

Patients and methods

Over a 2-year period there were 368 women who attended the urodynamic clinic with a primary complaint of urinary incontinence and had full clinical and urodynamic assessment. Each patient was examined and gave a full history; she was weighed in light street clothing to the nearest kilogram on a 'Fereday' pedestal weighing machine and her height was measured, without shoes, to the nearest centimetre. Each woman was assessed by cystourethroscopy, cystometry and uroflowmetry. A catheter specimen of urine obtained during the urodynamic study was examined microscopically and cultured to exclude urinary tract infection. Cystometry was performed with the patient in the sitting position and normal saline was infused at 37°C at 100 ml/min. A 10F double lumen catheter was used for filling and for measurement of intravesical pressure. Rectal pressure was measured with a fluid filled catheter. These pressures were recorded on a six-channel Lectromed MX6 Recorder with electronic subtraction for determining detrusor pressure. All urodynamic variables were defined according to the Standardisation Committee of the International Continence Society (Bates *et al.* 1979). Detrusor instability was diagnosed if uninhibited contractions occurred during filling, standing or with provocative testing, or if there was an increase in the baseline filling pressure above 15 cm of water. A diagnosis of genuine stress incontinence was made if there was a leakage of urine on cystometric assessment in the absence of a rise in detrusor pressure above 15 cm of water. If leakage was not demonstrated on provocative testing, patients who complained of persistent stress incontinence were still designated as having genuine stress incontinence as we would agree with others (Stallworthy 1971) that the patient who says she leaks is unlikely to be wrong, even though this could not be proven conclusively in the artificial circumstances of urodynamic investigation.

Obesity is a condition in which there is an excessive amount of body fat and this was assessed using both the relative weight and the body mass index.

Relative weight

This is expressed as a percentage of standard weight for age, height and sex derived from a survey conducted by the Office of Population Censuses and Surveys (1981). The patients were classified as follows: (i) underweight, less than 90% of average weight; (ii) normal, within 10% of average weight; (iii) overweight, 11–20% over average weight; (iv) obese, more than 20% above average weight.

Body mass index

Body mass-for-height indices have also been shown to be reliable indicators of adiposity (DHSS 1976). The most common is the Quetelet or body mass index which is the ratio mass (kg)/square of height (m^2). The body mass index was calculated for every patient. Statistical analysis used the Student's *t*-test and the Kolmogorov–Smirnov one-sample test.

Results

In this series of 368 patients, 232 (63%) were diagnosed as having genuine stress incontinence and 136 (27%) as having detrusor instability.

Table 1 shows the number of patients with genuine stress incontinence and detrusor

Table 1. Number of patients with genuine stress incontinence and detrusor instability according to weight classification compared with 'normal population'*

Weight class (in relation to average weight)	Genuine stress incontinence ($n = 232$) n %	Detrusor instability ($n = 136$) n %	Normal population* (%)
Obese (>20% over)	36 (15·5)	32 (23·5)	10·2
Overweight (11–20% over)	36 (15·5)	19 (14·0)	11·1
Normal (within 10%)	130 (56·1)	63 (46·3)	49·6
Underweight (>10% under)	30 (12·9)	22 (16·1)	29·1

* OPCS (1981).

Table 2. Distribution by age of patients with genuine stress incontinence and detrusor instability The mean (SD) body mass index of both incontinence groups was compared to that of the normal population (OPCS survey)

	Genuine stress incontinence ($n = 232$)			Detrusor instability ($n = 136$)			
Age group (years)	n	(%)	Body mass index (kg/m^2) Mean (SD)	n	(%)	Body mass index (kg/m^2) Mean (SD)	Mean body mass index in a general population*
15–29	9	(3·9)	24·7 (5·3)	9	(6·6)	23·1 (4·4)	22·5
30–39	44	(19·0)	24·0 (3·3)	20	(14·7)	25·9 (4·6)*	23·6
40–49	76	(32·8)	26·0 (3·7)*	48	(35·3)	26·6 (6·1)*	24·6
50–59	71	(30·6)	26·0 (4·5)	42	(30·9)	26·7 (3·8)*	25·4
>65	32	(13·8)	26·3 (3·5)	17	(12·5)	26·6 (4·8)	—

* Significantly different from a normal population (OPCS 1981) $P<0·01$.

instability according to their weight classification and compares the distribution by weight with a normal population (OPCS 1981). Obesity was more common in patients with genuine stress incontinence ($P<0{\cdot}01$) and detrusor instability ($P<0{\cdot}01$) than in the normal population (Kolmogorov–Smirnov one-sample test).

The mean body mass index in patients with genuine stress incontinence and detrusor instability was 25·8 and 26·1 respectively, compared with a mean value of 23·9 in the normal population.

Age

The patients' ages ranged from 15 to 85 years. As seen in Table 2, the age distribution of patients in this study with genuine stress incontinence and detrusor instability was similar; the highest percentage of patients was between 40 and 49 years of age in both groups. The mean body mass index was higher in both incontinence groups compared with a normal population (Table 2). There was a progressive rise with increasing age in both incontinent groups as well as in the normal population. No statistically significant difference was found in the mean body mass index between patients with genuine stress incontinence and those with detrusor instability.

Parity

The relation between the body mass index and parity is shown in Fig. 1; 93% of patients with genuine stress incontinence and 89% of those with detrusor instability were multiparous. Nulliparous patients with genuine stress incontinence had a higher mean body mass index (27·5, SD 4·6) than the multiparous (25·5, SD 3·7) ($0{\cdot}05<P<0{\cdot}01$), but in the detrusor instability group nulliparity was associated with a lower body mass index which rose with increasing parity (Fig. 1). The mean body mass index in nulliparous women with detrusor instability was 23·3 (SD 4·9) compared with 26·4 (SD 3·8) in multiparas ($0{\cdot}05<P<0{\cdot}1$).

Previous surgery

The frequency of previous surgery was similar in obese and non-obese patients with detrusor instability (19%). Of the 36 obese patients, 14 (39%) with genuine stress incontinence had previous incontinence surgery compared with 45 of 196 patients in the non-obese group (23%).

Patients with genuine stress incontinence who had had no previous incontinence surgery had a significantly lower body mass index (25·0) than patients with a previous history of incontinence

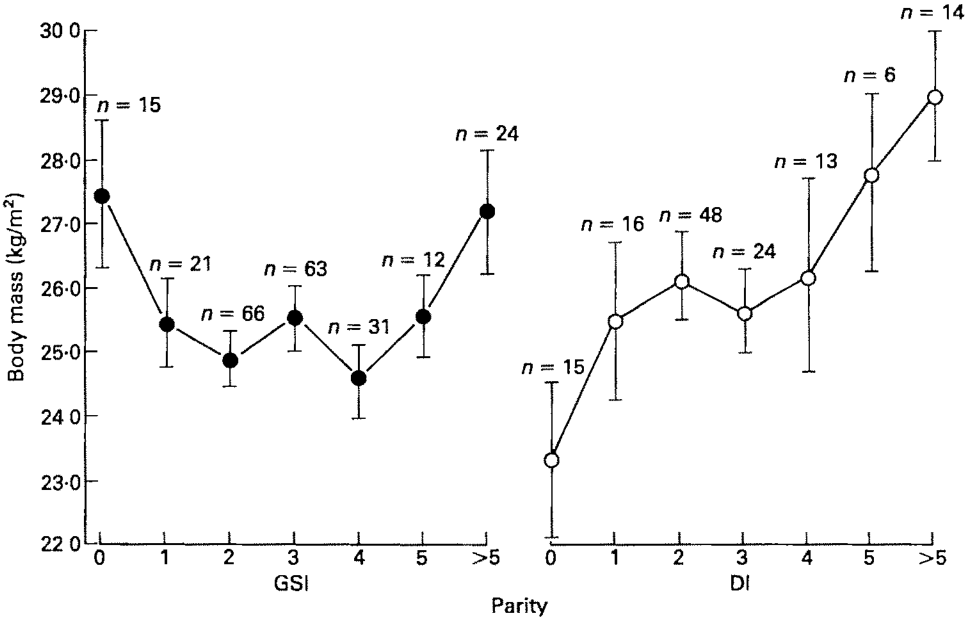

Fig. 1. Mean values ± SEM of body mass index (kg/m²) in patients with genuine stress incontinence (GSI) and detrusor instability (DI) according to parity.

surgery (26·9) ($P<0·01$). The body mass index was highest when more than one unsuccessful incontinence procedure had been performed previously (Table 3).

Urodynamic findings

The urodynamic findings on cystometry were compared between the obese and non-obese patients (Table 4) in both incontinent groups. There was no significant difference in any of the variables measured (two-sided Student's *t*-test).

Discussion

Urinary continence in women is maintained at rest by the tone of urethral smooth and striated muscle, blood vessel turgor and by the elasticity of the urethral connective tissue (Gosling *et al.* 1981). During stress and in the absence of detrusor activity the most important factor responsible for urethral closure is the proper transmission of intra-abdominal pressure to the bladder neck and proximal urethra (Enhorning 1961) with the levator ani providing an additional occlusive force in the distal urethra. The intra-abdominal position of the upper urethra is in turn dependent on its supporting structures, in particular the posterior pubourethral ligaments. It has been postulated that inefficiency in these ligaments may correlate with the development of genuine stress incontinence (Zacharin 1963). This weakness may be inherited or acquired secondary to damage during pregnancy or childbirth, menopausal atrophy or from chronically increased intra-abdominal pressure due to emphysema or chronic bronchitis. Intravesical pressure would appear to be markedly elevated in obese patients compared with thin patients (Warrell 1975). For continence to be maintained, any rise in intra-abdominal pressure would have to be equally transmitted to the proximal urethra or there would have to be an increase in resting urethral pressure or functional urethral length.

Surgical treatment of genuine stress incontinence is technically more difficult in obese patients especially when this is performed as an abdominal procedure and there is an increased risk of postoperative complications. Moreover, obesity may decrease the long-term effectiveness of incontinence surgery (Low 1967, Hodgkinson 1970) although Stanton *et al.* (1978) found neither pre-operative nor postoperative weight changes to be significant factors in failed incontinence surgery. In none of these studies

Table 3. Body mass index in patients with genuine stress incontinence according to number of previous operations

No. of previous incontinence operations	Body mass index	No. of patients	Age (years)	Parity
0	25·0 (3·6)	172	48·7 (13·5)	2·7 (1·7)
1	26·7 (4·1)*	50	52·5 (8·5)	3·5 (2·2)
>1	28·0 (3·4)**	10	51·7 (9·7)	2·8 (1·4)

Results are means (SD)

Significance of difference between patients with no previous surgery for incontinence * $P<0·01$, ** $P<0·02$

Table 4. Urodynamic findings in obese and non-obese patients with genuine stress incontinence and detrusor instability

	Genuine stress incontinence ($n = 232$)		Detrusor instability ($n = 136$)	
Variable	Obese ($n = 36$)	Non-obese ($n = 196$)	Obese ($n = 32$)	Non-obese ($n = 114$)
Residual urine (ml)	17·4 (20·8)	20·9 (31·7)	24·9 (29·2)	25·8 (39·9)
First sensation to void (ml)	210·0 (125·8)	208·6 (103·8)	166·1 (89·4)	137·3 (96·4)
Bladder capacity (ml)	473·9 (143·4)	504·0 (120·0)	430·3 (141·5)	409·1 (171·1)
Rise in detrusor pressure on filling or provocative testing (cm H_2O)	8·8 (3·1)	10·3 (3·2)	37·0 (21·5)	35·5 (17·7)
Peak flow rates (ml/s)	22·6 (9·7)	21·8 (11·1)	17·8 (10·3)	17·6 (12·5)

Results are means (SD).

was height taken into account in the assessment of relative weight. Our finding that patients with previous unsuccessful incontinence surgery were significantly more overweight than those with no previous surgery would seem to implicate obesity as a poor prognostic factor although the possibility of weight gain following failed surgery cannot be excluded.

In this study one quarter of all patients diagnosed with detrusor instability were obese, more than double the prevalence in the normal population. The aetiology of detrusor instability is obscure. In a small number of cases it may be secondary to an upper motor neurone lesion or recurrent bladder surgery. Psychological factors are obviously of considerable importance in the causation of idiopathic detrusor instability and this is borne out by the successful treatment of this condition by bladder retraining (Frewen 1972), biofeedback (Cardozo *et al.* 1978) and hypnotherapy (Freeman & Baxby 1982). Although anxiety may lead to overeating, the current view is that the morbidly obese do not show a unique personality pattern or have more psychological disturbances (Silverstone 1974). However, when Moore *et al.* (1962) analysed the relation between obesity and mental health, obese persons were significantly more immature, suspicious and rigid and 'a key trait and cause of their overeating was a defect in impulse control'. Although to our knowledge no similar psychological assessment has been performed on patients with detrusor instability it would be easy to see how this personality trait would also predominate in women with idiopathic detrusor instability where there is a loss of cortical inhibition resulting in involuntary detrusor contractions.

The prevalence of obesity increases with age, reaching a peak in the fifties and decreasing thereafter (Silverstone 1974). In this series of women with genuine stress incontinence and detrusor instability, the body mass index increased with age; obesity was more common in both incontinent groups than in the normal population at every age level.

Urinary incontinence is generally believed to be associated with parity (Thomas *et al.* 1980) and this was true in this study for both genuine stress incontinence (93%) and detrusor instability (89%). Obesity in women has been reported to increase with parity (Heliovaara & Aromaa 1981). Although this trend was evident in our group of patients with detrusor instability, nulliparous patients with genuine stress incontinence had a considerably higher body mass index than the multiparous. Obesity appears to be an important aetiological factor in nulliparous women contributing to the incompetence of the urethral sphincter which may already have a congenital or developmental weakness.

In this study no significant difference could be found in the urodynamic measurements between obese and non-obese women in either group. Further urodynamic and pathological studies are necessary to elucidate the effect of obesity on the anatomical and functional components which contribute to the continence of urine.

References

Bates, P., Bradley, W. E , Glenn, E., Griffiths, E., Melchior, H , Rowan, D., Stirling, A , Zinner, N. & Hald, T (1979) The standardization of terminology of lower urinary tract function. *J Urol* **121,** 551-554

Cardozo, L. D., Abrams, P. H., Stanton, S L. & Feneley, R C. I. (1978) Idiopathic bladder instability treated by biofeedback. *Br J Urol* **50,** 521-523.

DHSS/MRC (1976) *Report on Obesity* (James, W P T., Compiler), Her Majesty's Stationery Office, London, p. 4.

Enhorning, G (1961) Simultaneous recording of the intravesical and urethral pressure *Acta Chir Scand* **276 (Suppl.),** 1-68

Freeman, R. M. & Baxby, K. (1982) Hypnotherapy for incontinence caused by the unstable detrusor *Br Med J* **284,** 1831-1834.

Frewen, W. K. (1972) Urgency incontinence. Review of 100 cases. *J Obstet Gynaecol Br Commonw* **79,** 77-79

Gosling, J , Dixon, J. S., Critchley, H O D & Thompson, S. A. (1981) A comparative study of the human external sphincter and periurethral levator ani muscles *Br J Urol* **53,** 35-41.

Heliovaara, M. & Aromaa, A. (1981) Parity and obesity. *J Epidemiol Community Health* **35,** 197-199.

Hodgkinson, C. P (1970) Stress urinary incontinence—1970. *Am J Obstet Gynecol* **108,** 1141-1168.

Low, J. A (1967) Management of anatomic urinary incontinence by vaginal repair. *Am J Obstet Gynecol* **97,** 308-315.

Moore, M. E., Stunkard, A. & Srole, L. (1962) Obesity, social class and mental illness. *JAMA* **181,** 962-966.

Office of Population Censuses and Surveys (1981)

Adult heights and weights survey *OPCS Monitor SS* **81,** 1-10.

Silverstone, T. (1974) Psychological and social factors in the pathogenesis of obesity In *Obesity* (Burlend, W L., Samuel, P. D & Yudkin, J., eds), Churchill Livingstone, Edinburgh, p 105.

Stallworthy, J. A (1971) Prolapse Aetiology and diagnosis. *Br Med J* **1,** 499-500.

Stanton, S. L., Cardozo, L., Williams, J. E , Ritchie, D. & Allan, V. (1978) Clinical and urodynamic features of failed incontinence surgery in the female *Obstet Gynecol* **51,** 515-520

Thomas, T M., Plymat, K R., Blannin, J. & Meade, T W. (1980) Prevalence of urinary incontinence. *Br Med J* **281,** 1243-1245.

Warrell, D W (1975) Incontinence of urine in women *Nursing Times* 1470-1473

Zacharin, R F. (1963) The suspensory mechanism of the female urethra. *J Anat* **97,** 423-427.

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Retrieval of intrauterine contraceptive devices with missing tails, using Lamicel

NICHOLAS JOHNSON, JACK MOODLEY

Summary. Preliminary cervical dilatation using Lamicel, followed by relatively painless uterine probing was successful in removing 30 of 31 contraceptive devices that had not been removable in the outpatient clinic. This technique is simple, safe, inexpensive and well tolerated. It can be utilized to retrieve intrauterine contraceptive devices with missing tails when other conventional clinic procedures fail.

The major problems of the intrauterine contraceptive device (IUCD) are pregnancy, pelvic inflammatory disease and 'loss of the tails'. Failure to detect the tail of an IUCD during a vaginal examination implies that the device may no longer be within the uterus or that the tail has broken off or has migrated up the cervical canal.

Leaving the threadless device *in situ* is not usually acceptable and the threads seldom reappear (Basu 1977). There are various techniques to remove devices which are within the uterus but have no visible threads. The cervical canal may be explored with small forceps (Ansari 1974), the uterine cavity may be explored with a hooked or spiral fine plastic curette (Ansari & Hoffman 1982) or the gynaecologist may proceed to a mechanical cervical dilatation and uterine exploration under general anaesthesia. If the cervix could be dilated painlessly the uterine cavity could be formally explored and devices removed without anaesthesia.

A new transcervical tent marketed as Lamicel capable of dilating the cervix in late pregnancy has recently become available. Lamicel (Cabot Medical, Langhorne, USA) is a polyvinyl alcohol sponge impregnated with magnesium sulphate and compressed to form a 3 mm diameter firm cylindrical rod (Johnson *et al.* 1985; Wheeler & Schneider 1983). Its mechanism of action is unknown. The popular belief is that the sponge, when placed in the cervical canal, expands as it absorbs water thus producing a gentle mechanical dilatation. No associated complications have been described.

Patients and methods

Only patients referred specifically to the author by a gynaecologist or the hospital family planning clinic with a diagnosis of 'lost loop requiring removal under anaesthesia' were offered Lamicel and subsequent uterine exploration. No patients were refused. Informed consent was obtained and the patients were warned to expect discomfort and possible failure.

The uterus was investigated with ultrasound to confirm the location of the device. The cervix was displayed and an attempt was made to retrieve the device conventionally using Bozeman's forceps and by passing a fine barbed plastic thread retriever. If the device remained intrauterine, a 3 mm Lamicel, held by its flat collar in sponge forceps was passed transcervically. Occasionally the anterior lip of the cervix had to be grasped with a vulsellum to facilitate entry of the tip of the Lamicel through the internal os. Neither analgesia, prophylactic antibiotics nor a paracervical block were used. No restrictions were placed on the subsequent activity of the patient. Several hours after inserting the Lamicel (depending on patient and oper-

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Department of Obstetrics and Gynaecology,
University of Natal, PO Box 17039, Congella 4013,
Durban, Republic of South Africa
NICHOLAS JOHNSON *Registrar*
JACK MOODLEY *Professor*

Correspondence: N. Johnson, Woodland Avenue, Tywardreath, Cornwall PL24 2PL

ator convenience) the device was withdrawn by traction on the sponge strings. With the patient in the lithotomy position and the cervix exposed, the anterior lip was gently grasped with a vulsellum. A small uterine curette (5 mm wide) was passed, the cavity explored and the loop delivered.

Cervical dilatation was measured with Hegar dilators. Pain, defined as an unpleasant sensation during any part of the procedure, was considered to be present or absent. Its presence was measured subjectively or objectively (either a wince, sharp intake of breath, or, as in one case, a moan). Statistical analysis used the non-parametric Mann-Whitney test.

Results

Forty-seven patients were studied. Three patients were excluded, either because of pelvic pathology or because they did not want to be included. Eleven loops could be removed conventionally. Two patients had such tight cervical canals that the 3 mm diameter Lamicel could not be passed.

The remaining 31 patients were treated with Lamicel Three were of Indian origin whilst the remainder were black Africans. The majority were of low socio-economic standing. The technique failed only in one patient; this was not due to the use of the Lamicel as despite good cervical dilatation (at least 7mm), the IUCD could not be located. At a later date hysteroscopy under general anaesthesia was performed. Only the tip of a Lippes Loop could be seen at the fundus. The remainder was embedded within the wall of the uterus. Most patients found the technique acceptable. Of the 30 patients in whom the Lamicel facilitated removal of the IUCD, two were undecided whether or not a general anaesthetic would have been a preferable experience. Both these patients initially had tight cervices. One was menopausal and the other was an older nulliparous woman. Subsequent dilatation was poor and consequently it was difficult to remove the IUCD. The other 28 patients were delighted to have avoided admission to hospital and anaesthesia.

Pain during removal of the device is summarized in Table 1. Three patients (10%) felt the procedure was akin to labour pains but tolerable, six patients felt that the pain was worse than dysmenorrhoea but preferable to labour and a further six described the pain as no worse than dysmenorrhoea or venepuncture. Half (15) of the patients declared that the procedure was painless and they showed no objective signs of pain or discomfort.

Insertion of the sponge was painful in nine (30%) patients. The discomfort experienced

Table 1. Characteristics of 30 patients having an intrauterine contraceptive device removed

	n	Number experiencing pain during IUCD removal	Number of painless IUCD removals	Final cervical dilation (mm) mean (SD)
Nulliparous patients	6	6	0	6 2 (0·9)
Pre-menopausal parous patients	22	7	15	7·1 (0·3)
Menopausal parous patients	2	2	0	5 5 (0·5)
Total	30	15	15	6·8 (0·6)
Insertion painful (cervix initially tight)	9	9	0	6·0 (0·8)
Insertion comfortable	21	6	15	7·2 (0·5)
Type of device				
Lippes Loop	5	4	1	
Majzlin Spring	1	1	0	
Copper T or 7	7	4	3	
Gravigard	16	5	11	
Dalkon Shield	1	1	0	
Thread retracted cranially	7	1	6	
Thread absent	23	14	9	
Thread broken by previous removal attempt	13/23	8	5	

during the insertion of a 3 mm diameter Lamicel was directly related to the initial state of the cervix. In these patients, the final dilatation achieved was significantly less than in those where insertion was painless (Table 1) ($P<0{\cdot}02$). Provided the Lamicel remained in the cervical canal for at least 3·5 h, little was gained by prolonging this interval (Fig. 1). No patients experienced bleeding subsequently that was greater than a normal period; none complained of pain other than the initial short-lived uterine pain and low pelvic ache and none had signs or symptoms of pelvic infection. On examination at follow-up all had healthy closed cervices and non-tender pelvic organs.

Discussion

In the present series, the technique described was successful in removing 30 out of 31 'lost' IUCDs. However, it is important to point out that the patients attending our hospital are Zulu-speaking Africans. This group are generally of low socio-economic status, used to hardship and well adjusted to pain and discomfort. They are motivated towards avoiding admission to hospital and anaesthesia for cultural and economic reasons. The overwhelming acceptance of this procedure must be judged in this light

The pain on insertion of the sponge is directly related to the initial state of the cervix rather than to the patient's personality or to her perception of pain. If the cervix will accommodate a 3 mm device then the passage of the sponge is a relatively painless matter. In contrast, if the cervical canal has a diameter of less than 3 mm, not only does the anterior lip of the cervix have to be grasped with a vulsellum but the sponge has to be forcefully passed. Nicolaides *et al.* (1983) passed 5-mm Lamicels during early pregnancy and reported that 33% of the patients experienced 'discomfort'. No other comparative literature is available.

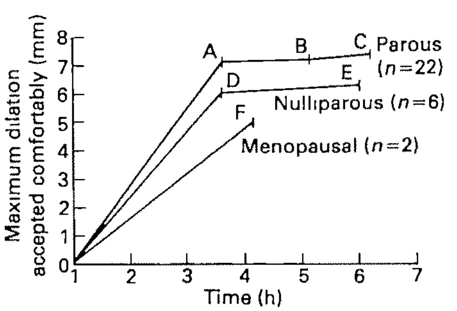

Fig. 1. Final state of the cervix after mechanical dilatation with Lamicel Mean (SD) values for cervical dilatation at intermediate times as shown were: (A) 7·0 (0·4) mm (n=11); (B) 7·0 (0·6) mm (n=6); (C) 7·2 (0·2) mm (n=5); (D) 6 mm (n=2); (E) 6·25 (1·1) mm (n=4), (F) 5·0 mm (n=2)

If the cervix initially accommodated a 3 mm diameter tent comfortably then the subsequent dilatation achieved was significantly greater than that achieved if the cervix was initially tight (e.g. in nulliparous or menopausal women). The final dilatation achieved is not dependent on the length of time that the Lamicel is *in situ* but on the initial state of the cervix. Consequently, removal of a contraceptive device from parous patients was technically easier, took less time and was more acceptable

Where the thread of the IUCD had been pulled off during a previous attempt at removal the patients were more likely to experience discomfort than those in whom the thread had retracted cranially or had been cut too short. This is hardly surprising as a device which remains intrauterine despite traction sufficiently great to break the junction of plastic and string is most likely to be partly embedded in the uterine wall. Such devices need to be dislodged before extraction is possible, a manoeuvre which adds to the patient's discomfort and to surgical time.

Patient selection will affect the number of IUCDs that are difficult to retrieve. Nulliparae with tight cervices harbouring old-fashioned devices will prefer to avoid an anaesthetic, but the operator may be more at ease with an unconscious patient. The operator must be patient and always gentle. Retrospective analysis of the results in chronological order illustrates that the first patients were not completely comfortable and this may be related to the operator's inexperience with the technique.

Hale & Pion (1972) succeeded in removing some IUCDs using *Laminaria digitata.* They obtained sufficient cervical dilatation to pass fine forceps into the cervical canal but they did not formally explore the uterine cavity. The use of transcervical tents became unpopular, particularly in the USA, with reports of associated sepsis (Baer 1882), endometritis (Kazzi *et al.* 1982), uterine perforation, cervical tears (Lee 1885), migration of the tent into the uterus, entrapment of the tent (dumbelling) and slow, uneven and unreliable dilatation of the cervix with the requirement of several insertions and overnight hospitalization (Ott 1977). The new tent (Lamicel) has not yet been associated with such complications. It is an effective and safe method with which to dilate the non-pregnant cervix and thus make the uterine cavity available for exploration. Parous patients or those in whom the tail of the IUCD had retracted cranially and those who were fortunate enough to be given a modern device were most easily satisfied.

References

Ansari, A. H. (1974) Diagnosis and management of intrauterine devices with missing tail *Obstet Gynecol* **44,** 727-734

Ansari, A H & Hoffman, D. N (1982) Retrieval of IUCD with missing tail by means of a plastic spiral curette (Mi-Mark) *Am J Obstet Gynecol* **142,** 1061-1062.

Baer, B F (1882) Death after dilatation of the cervix uteri with a laminaria tent *Proc Obstet Soc Phil* 25th February, p 218

Basu, H. K (1977) Missing tails (letter.) *Br Med J* **i,** 713.

Hale, R. W. & Pion, R J. (1972) Laminaria: An underutilized clinical adjunct. *Clin Obstet Gynecol* **15,** 829-850.

Johnson, I. R , MacPherson, M. B. A., Welch, C. C. & Filshie, G. M. (1985) A comparison of Lamicel and prostaglandin E_2 vaginal gel for cervical ripening before induction of labor. *Am J Obstet Gynecol* **151,** 604-607.

Kazzi, G. M , Bottoms, S F. & Rosen, M G (1982) Efficacy and safety for Laminaria digitata for preinduction ripening of the cervix. *Obstet Gynecol* **60,** 440-443.

Lee, C C. (1885) Perforation of the cervix uteri by a Laminaria tent *NY Med J* **July,** 109.

Nicolaides, K. H., Welsh, C. C., MacPherson, M. B. A., Johnson, I. R. & Filshie, G. M. (1983) Lamicel: a new technique for cervical dilatation before first trimester abortion *Br J Obstet Gynaecol* **90,** 475-479

Ott, E. R (1977) Pregnancy termination· cervical dilatation. A review. *Popul Rep* [F] **no. 6,** F85-F103.

Wheeler, R. G. & Schneider, K (1983) Properties and safety of cervical dilators *Am J Obstet Gynecol* **146,** 597-601.

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SHORT COMMUNICATIONS

A purpose-designed cannula for transcervical chorion villus aspiration

D. T. Y. Liu *Senior Lecturer/Consultant,* B. Jeavons *Research Sister,* C. Preston *Research Sister* & E. Slater *Medical Physicist, Departments of Obstetrics & Gynaecology and Medical Physics, City Hospital, Queen's Medical Centre, Nottingham*

We describe our experience with a sampler designed specifically for ultrasound-guided transcervical aspiration of chorionic villi. This sampling device is a round-ended non-malleable 14-gauge (2 mm diameter) metal cannula 21 cm in length with the distal 3 cm angulated 30° (Fig. 1). Placed either on the left or right side of the cannula and 0·3 cm from the tip is a tear-drop shaped opening (1·5 mm × 2 mm) with the point directed towards the operator to introduce a pincer action which cuts the villi during aspiration. The pincer action minimizes trauma by reducing the need for excessive to and fro movements or 'hoovering' (Ward *et al.* 1983) to detach villi for collection. A further refinement is a 3 mm flattened area at the tip which reflects ultrasound and facilitates cannula tip localization.

The efficacy of this sampling device was tested in comparison with a similar length 16-gauge (1·6 mm diameter) round-ended malleable metal cannula where the circular collecting portal was on the dorsal surface 0·3 cm from the tip. This type of cannula was chosen for comparison because it is reported to be more efficient than polythene cannulae (MacKenzie *et al.* 1986).

The study

In the first part of the study 75 women undergoing therapeutic abortion of a singleton pregnancy between 8 and 12 weeks gestation gave informed consent to participate. All sampling was performed by the same operator (D.T.Y.L.) using one of the two cannulae (14- or 16-gauge), allocated at random on an alternate basis, for a maximum of two attempts after the patients were anaesthetized for surgery. Where

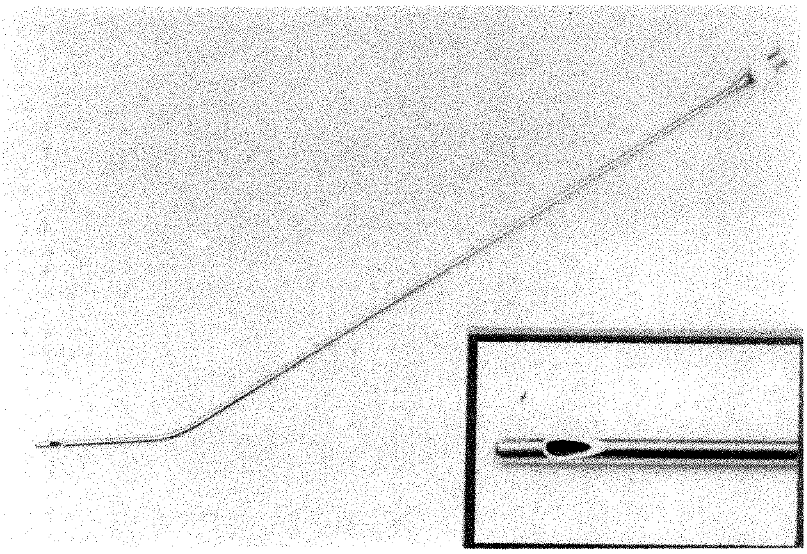

Fig. 1. The sampler (magnified tip shown at inset).

Table 1. Characteristics of women having transcervical villus sampling with two types of cannulae

	Type of cannula	
Characteristic	14-gauge	16-gauge
No. of women	41	34
Primigravidae	12	13
Mean age (years)	28·9	26·8
Gestation (weeks) range	8–12	8·5–12
Placental site		
Anterior	23	9
Posterior	16	17
Enveloping	2	8
Factors making insertion difficult	2	0

the allocation was for the 14-gauge cannula, selection of one with a right or left opening was governed by position of the placental site.

In the second part of the study the 14-gauge cannula was used in 55 consecutive patients for diagnostic chorion villus sampling.

The χ^2 test was used to compare proportions.

Results

Table 1 details the clinical characteristics of the two groups of women investigated in the first part of the study. The specially designed sampler with its wider gauge and fixed angulation provided a more secure feeling of control and was readily manipulated to all placental sites. Neither uterine sound nor volsellum was required in any of the patients. An adequate amount of chorionic villi (≥ 10 mg wet weight) was obtained from all patients after two attempts with the 14-gauge sampler. This was significantly better ($P<0·001$) than the 65% success rate after two attempts with the 16-gauge cannula. Complication rates were comparable for the two cannulae.

Diagnostic chorion villus sampling was successful with the purpose-designed cannulae in all 55 women. Bleeding after the diagnostic procedure occurred less often than the 60% reported by Warren *et al.* (1987) and the miscarriage rate is acceptable (Laird Jackson, *Chorionic Villus Sampling Newsletter* 1986).

Comments

The prime objective of this study was to produce a cannula for transcervical aspiration of chorionic villi which the practised obstetrician and in particular the trainee will find reliable and easy to use. In our experience this specially designed sampler fulfilled these conditions and it now merits independent assessment.

References

Mackenzie, W. E., Holmes, D. S., Webb, W. D. B., Whitehouse, C. & Newton, J. R. (1986) A randomised study of three cannulae for transcervical chorion villus sampling. *Am J Obstet Gynecol* **154,** 34-39.

Ward, R. H. T., Modell, B., Petrou, M., Karagozlu, F. & Douratsos, E. (1983) Method of sampling chorionic villi in first trimester of pregnancy under guidance of real-time ultrasound. *Br Med J* **286,** 1542-1544.

Warren, R. C., Mackenzie, C. F., Kerney, L. & Rodeck, C. H. (1987) Transcervical chorion villus aspiration by a single operator technique. In *Chorion Villus Sampling* (Liu, D. T. Y., Symonds, E. M. & Golbus, M., eds), Chapman & Hall, London, pp., 65-72.

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Incorporating "Patient Education Reports"

PATIENT EDUCATION AND COUNSELING

An Interdisciplinary Journal for Patient Education Researchers and Managers

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Aims and Scope

Patient Education and Counseling is an interdisciplinary, international journal for patient education researchers, managers, and others involved in patient education and counseling. The journal covers educational and counseling activities conducted both in in-patient and out-patient settings. Its aim is to provide a forum for applied research, and to promote examination of administrative issues involved with the delivery of patient education and counseling services.

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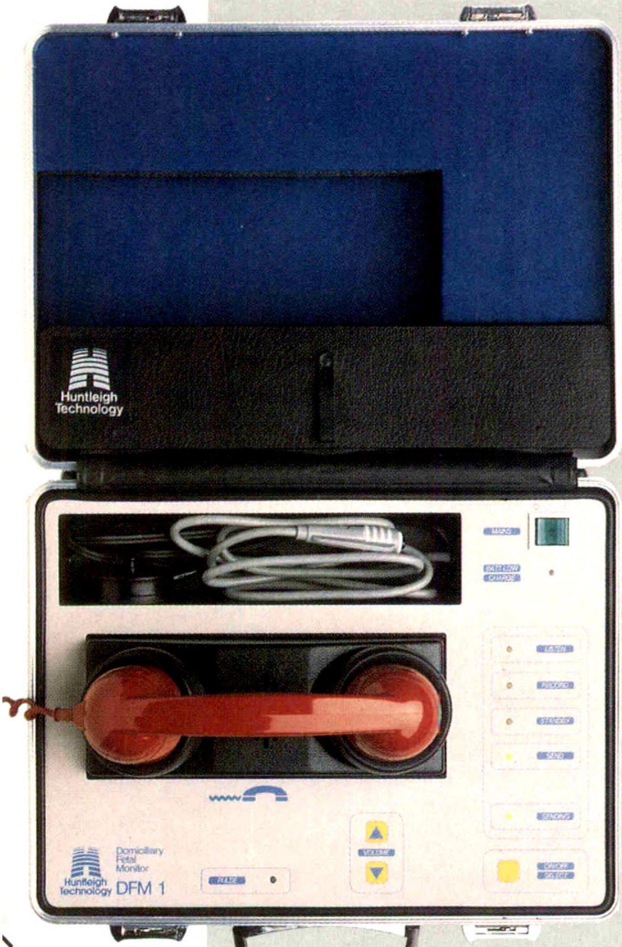

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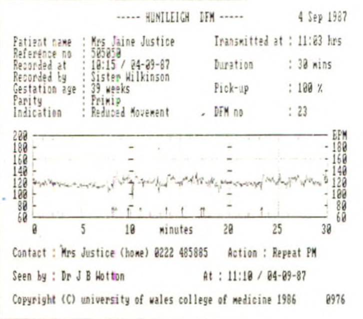

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----- HUNILEIGH DFM -----                    4 Sep 1987

Patient name   : Mrs Jaine Justice      Transmitted at : 11:03 hrs
Reference no   : 505050
Recorded at    : 10:15 / 04-09-87       Duration       : 30 mins
Recorded by    : Sister Wilkinson
Gestation age  : 39 weeks               Pick-up        : 100 %
Parity         : Primip
Indication     : Reduced Movement     . DFM no         : 23

Contact : Mrs Justice (home) 0222 485885    Action : Repeat PM

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British Journal of Obstetrics and Gynaecology
January 1988, Vol. 95, pp. 103–107

CORRESPONDENCE

In utero meconium aspiration: an unpreventable cause of neonatal death

Dear Sir,

Byrne & Gau [*Br J Obstet Gynaecol* (1987) **94**, 813–814] claim that in utero meconium aspiration is an unpreventable cause of neonatal death. I disagree and for more than a generation, I have recommended narcotizing or sedating the fetus exposed to heavy in utero meconium. In my experience, the incidence of severe meconium aspiration in the newborn is markedly increased when the mother has received no narcotics during labour (Goodlin 1968, 1970, 1974, 1980, 1984).

Robert C. Goodlin
Professor
Obstetrics and Gynecology
University of Colorado Health Sciences Center
4200 East Ninth Avenue
Denver, Colorado 80262, USA

References

Byrne, D. L. & Gau, G. (1987) In utero meconium aspiration: an unpreventable cause of neonatal death. *Br J Obstet Gynaecol* **94**, 813-814.

Goodlin, R. C. (1968) Meconium aspiration. *Obstet Gynecol* **32**, 94-95.

Goodlin, R. C. (1970) Suppression of fetal breathing to prevent aspiration of meconium. *Obstet Gynecol* **36**, 944-947.

Goodlin, R. C. (1974) Fetal sedation. *Anesth Analg* **43**, 297.

Goodlin, R. C. (1980) Low-risk obstetric care for low risk mothers. *Lancet* **i**, 1017-1019.

Goodlin, R. C. (1984) Detrimental perinatal associations with increased fetal reactivity. *Am J Obstet Gynecol* **149**, 801-803

Authors' reply

Dear Sir,

In the case presented we postulated that the meconium aspiration occurred early, probably before the onset of labour. Hence, any intervention in labour, such as sedation of the fetus, would be too late to change the outcome, in this case neonatal death.

In an attempt to illustrate predictive factors of meconium aspiration we have recently completed a review of 25 302 deliveries at Queen Charlotte's Maternity Hospital (Coltart & Byrne, unpublished data). We could not find a correlation between pethidine use in labour and prevention of meconium aspiration. However, we did find a significant correlation between pethidine use and the absence of meconium-stained amniotic fluid. Whether this reflects a direct effect of pethidine on meconium passage, or the cautious nature with which narcotics are used in patients with meconium-stained amniotic fluid is not clear at present.

Whilst we applaud any method of prevention of meconium aspiration we are concerned that sedation of the potentially compromised fetus will worsen the neonatal status (Kariniemi & Rosti 1986) at birth, and augment hypoxic damage (Kuhnert *et al.* 1985).

We also feel that such action would not gain widespread obstetric support in this country as has been Professor Goodlin's experience in North America (Goodlin 1974).

D. L. Byrne
G. Gau
Queen Charlotte's Maternity Hospital
Goldhawk Road
London W6 0XG

References

Goodlin, R. C. (1974) Fetal sedation *Anesth Analg* **43**, 297.

Kariniemi, V. & Rosti, J (1986) Intramuscular pethidine during labor associated with metabolic acidosis in the newborn. *J Perinat Med* **14**, 131-135.

Kuhnert, B. R., Kuhnert, P M., Philipson, E H. & Syracuse, B. S. (1985) Disposition of meperidine

Prolactin measurement in the investigation of infertility in women with a normal menstrual cycle

Dear Sir,

Dr Glazener and colleagues [*Br J Obstet Gynaecol* (1987) **94**, 535–538] refer to the infrequently observed syndrome of hyperprolactinaemic luteal deficiency and infertility in the normally menstruating woman. It is interesting to note the recent report by Kauppila *et al.* (1987) of isolated hypoprolactinaemia with normal menstruation causing similar luteal and fertility problems. Thus, in very rare circumstances, the problem may be a case of too little rather than too much.

Christopher Fitzpatrick
Senior House Officer
Department of Obstetrics & Gynaecology
National Maternity Hospital
Holles Street
Dublin 2, Ireland

References

Glazener, C M. A., Kelly, N. J & Hull, M. G. R. (1987) Prolactin measurement in the investigation of infertility in women with a normal menstrual cycle *Br J Obstet Gynaecol* **94**, 535-538

Kauppila, A , Chatelain, P., Kirkinen, P., Kivinen, S & Ruokonen, A (1987) Isolated prolactin deficiency in a woman with puerperal alactogenesis *J Clin Endocrinol Metab* **64**, 309-312.

Authors' reply

Dear Sir,

Dr Fitzpatrick has drawn attention to the possibility of isolated hypoprolactinaemia causing luteal and fertility problems. However, the patient described in the article by Kauppila *et al.* (1987) presented primarily because of failure of lactation after her first pregnancy. There was no suggestion that she had infertility while trying to conceive that pregnancy, although she took 3 years to conceive her second pregnancy and in two investigated cycles had short luteal phases although hormonal concentrations were normal. Clomiphene made no difference to her cycle length. Again she conceived spontaneously some 2 years after the cycle that was treated with clomiphene.

Turkington (1972) described two similar case reports of isolated hypoprolactinaemia. The two reported women also presented with failure of lactation in the puerperium and there was no suggestion of fertility problems in either of them.

On review of our own patients we found two whose prolactin concentrations were at the lower limit of sensitivity of the assay (39 i.u./l). One woman conceived spontaneously in her first cycle of observation. The other had normal progesterone concentrations (>28 nmol/l) in seven observed non-conception cycles after which she conceived spontaneously.

In conclusion, we do not feel that there is any clear evidence to support a relation between hypoprolactinaemia and infertility.

C. M. A. Glazener
Clinical Research Registrar
Department of Obstetrics and Gynaecology
Bristol Maternity Hospital
Bristol BS2 8EG

References

Kauppila, A., Chatelain, P., Kirkinen, P., Kivinen, S. & Ruokonen, A (1987) Isolated prolactin deficiency in a woman with puerperal alactogenesis. *J Clin Endocrinol Metab* **64**, 309-312.

Turkington, R. W. (1972) Phenothiazine stimulation test for prolactin reserve: the syndrome of isolated prolactin deficiency *J Clin Endocrinol Metab* **34**, 247-251

A randomized control study of oxytocin augmentation of labour. 1. Obstetric outcome

Dear Sir,

In their small randomized control study of oxytocin augmentation of labour *[Br J Obstet Gynaecol* (1987), **94**, 512–517], Drs Bidgood and Steer conclude that the results do not support the belief that the active management of labour minimizes the need for caesarean section for dystocia (O'Driscoll *et al.* 1984). The evidence presented does not permit the conclusion drawn.

The success of active management is not based on the 'wholesale use of oxytocin'. The basic principles of active management are first, a strict diagnosis of labour and second, the early diagnosis and prompt treatment of dystocia in primigravidae (O'Driscoll *et al* 1984; Turner *et al.* 1986). The criteria for the diagnosis of labour in this study differ from those of active management and, more importantly, the study describes the late diagnosis and delayed treatment of dystocia with varying oxytocin infusions.

Randomized control trials based on small numbers are lacking in power and may easily fail to detect important therapeutic benefits (Altman 1983; Chalmers 1984; Bryce & Enkin 1985). Based on their statistical calculations, the authors admit that they intended entering 150 patients into the study but succeeded in entering only 60. In addition, 58 of the 60 women studied required epidural analgesia, which is associated with an increase in both operative deliveries (Kadar 1985) and oxytocin requirements (Goodfellow *et al.* 1983). The results presented cannot be extrapolated to primigravidae who do not receive epidural analgesia in labour.

In the discussion, the authors claim that an overall intrapartum caesarean section rate of 8·9% was achieved with an augmentation rate in spontaneous primigravid labour of approximately 5%. However, it is the intrapartum section rate in spontaneous primigravid labour which should have been stated. We have applied the principles of active management in another London hospital (Turner *et al.* 1986). This has been associated with a reduction in the caesarean section rate in primigravidae without any evidence that the fetal outcome is worse (Turner *et al.* 1987). The intrapartum caesarean section rate was 3·4% in 614 consecutive primigravidae managed actively in spontaneous labour and, in the absence of occipito-posterior position, none of the women required a section for failure to progress

The success of the active management of labour in maintaining a low rate of caesarean childbirth in over 150 000 women in Dublin cannot be dismissed on the evidence presented in this study of 60 women. We agree that properly constructed studies are needed to convince the unconvinced of the benefits of active management but this paper does little to resolve the debate.

Michael J. Turner
Research Fellow and Honorary Senior Registrar
Institute of Obstetrics and Gynaecology
Hammersmith Hospital
Du Cane Road, London W12 0HS
Harry Gordon
Consultant Obstetrician
Maternity Department
Northwick Park Hospital
Harrow, Middlesex HA1 3UJ

References

Altman, D G (1983) Size of clinical trials. *Br Med J* **286,** 1842-1843.

Bryce, R. L. & Enkin, M W. (1985) Six myths about controlled trials in perinatal medicine *Am J Obstet Gynecol* **151,** 707-710

Chalmers, I (1984) Confronting Cochrane's challenge to obstetrics *Br J Obstet Gynaecol* **91,** 721-723

Goodfellow, C F, Hull, M G R., Swaab, D F, Dogterom, J. & Buijs, R M. (1983) Oxytocin deficiency at delivery with epidural analgesia *Br J Obstet Gynaecol* **90,** 214-219

Kadar, N (1985) The second stage In *The Management of Labour* (Studd, J , ed), Blackwell Scientific Publications, London, pp 268-286

O'Driscoll, K , Foley, M & MacDonald, D (1984) Active management of labor as an alternative to cesarean section for dystocia *Obstet Gynecol* **63,** 485-490.

Turner, M. J., Webb, J. B & Gordon, H. (1986) Active management of labour in primigravidae. *J Obstet Gynaecol* **7,** 79-84

Turner, M. J., Fox, R & Gordon, H. (1987) Active management of labour *Lancet* **i,** 753-754.

Dear Sir,

The small number of patients in the study of the use of oxytocin in labour, reported by Dr Bidgood and Dr Steer [*Br J Obstet Gynaecol* (1987) **94,** 512-517] does not allow any valid conclusions to be drawn. Emphasis is laid on the prevalence of uterine hyperstimulation which occurred only when high-dose oxytocin was infused. Seven of 21 women who received oxytocin at a rate of 7 mU/min developed hyperstimulation within 15 min of starting the infusion Hyperstimulation was defined as the observation of more than seven contractions in 15 min or a rising basal tone of >1·33 kPa pressure. It is not stated whether the uterine contractions were noted on abdominal palpation or observed from an external cardiotocograph or as a result of intrauterine pressure recording.

In the National Maternity Hospital hyperstimulation is diagnosed when there are more than seven palpable uterine contractions occurring in any 15-min period. A contraction is defined as a tightening of the uterus which continues for ≥20 s When contractions last <20 s it may be the abdominal muscles rather than the uterus that is felt to be contracting. When an oxytocin infusion is administered the attendant student midwife counts the number of contractions for every 15 min interval and records them on the partogram.

In three of the seven index cases the diagnosis of hyperstimulation was not sustained because the condition resolved spontaneously. In another three, spontaneous resolution was not awaited because the regimen was changed from a high-dose to a low-dose infusion. In the remaining patient where fetal distress was associated with hyperstimulation, the fetal distress persisted despite the withdrawal of the oxytocin and would appear to be unrelated to the use of oxytocin.

The active management of labour has been standard practice in the National Maternity Hospital since 1969 (O'Driscoll & Meagher 1986). Since 1 January 1984 all primigravid and multigravid partograms have been carefully analysed by us on a continuous daily basis. During those 3 years a total of 7983 primigravidae were delivered and 3181 (39%) received oxytocin, either to induce labour or to accelerate slow labour. There was no case of uterine hyperstimulation because no woman in labour had more than seven palpable uterine contractions in any 15-min period.

The benefits of this policy for women in labour are unchallenged.

Prolonged labour, defined as an admission-to-delivery interval of >12 h, occurred in 260 patients (3%) and consequently, only 682 women (8%) received epidural analgesia. The overall rate of caesarean section in primigravidae was 6·2% (501 patients). The total number who were delivered by caesarean section for dystocia was 120 (1·6%)

These results are presented to refute the claim that the high-dose oxytocin used to correct inefficient uterine action in the National Maternity Hospital is inherently unsafe. The early recognition and the prompt correction of inefficient uterine action is the keystone to the active management of labour. Obsession with the mechanics of oxytocin administration sometimes leads to a delay in diagnosis and inadequate treatment.

John Stronge
Master
Ruth Connolly
Assistant Master
National Maternity Hospital
Holles Street
Dublin 2

Reference

O'Driscoll, K & Meagher, D. (1986) *The Active Management of Labour* Baillière Tindall, London.

Authors' replies

Dear Sir,

With reference to the letter from Messrs Turner and Gordon, we would point out that we did not claim that our data refuted the value of the active management of labour but merely did not support the use of the high dose rates of oxytocin which are often recommended as part of the regimen. In addition, we were surprised to find that in more than 50% of cases without oxytocin augmentation, there was a spontaneous increase in uterine activity and cervical dilatation rate which resulted in a vaginal delivery. In the light of our results we feel that further research is justified so as to distinguish between women who will benefit from oxytocin infusion and those who can safely be left to labour and deliver unaided. We are pleased that Messrs Turner and Gordon agree with us about the need for further properly constructed studies; while we may not have resolved the debate we have at least stimulated it.

With reference to the letter from Drs Stronge and Connolly, we do not accept that there are no valid conclusions which can be drawn from our trial. We have shown, for example, that intravenous oxytocin infusion significantly increases the level of uterine activity in slow labour of spontaneous onset, and that this is associated with a significantly increased rate of cervical dilatation. This might have been expected *a priori*, but perhaps less expected was the finding that at the beginning of the study, 18 women (30%) already had levels of uterine activity above the mean for unselected spontaneous labour, and that even without treatment uterine activity rose significantly with time by over 30%, from 947 kPas/15 min to 1291 kPas/15 min. This suggests that in many women with slow labour, oxytocin augmentation is either inappropriate or unnecessary.

We do, however, agree with Drs Stronge and Connolly that the observation of uterine hyperstimulation in 37% of the group given high dose oxytocin is important. As we stated in our methods section 'an initial examination was performed by K.A.B ... to insert a Sonicaid-Gaeltec intrauterine catheter to measure intrauterine pressure'. We consider that this technique allows reliable measurement of uterine activity, including hyperstimulation (Steer *et al.* 1978). Our diagnosis of hyperstimulation was based on that of Caldeyro-Barcia *et al.* (1957), who suggested a maximum physiological value of uterine activity of 250 Montevideo units (MU) equivalent to 2000 kPas/15 min. He found that in women having labour induced by oxytocin infusion 'the physiological limits are surpassed when the infusion rate is increased to 32 mU/min'. Poseiro & Noriega-Guerra (1961) added the further important observation that hyperstimulation (>5 contractions/10 min and a rise in baseline tone of >12 mmHg) usually required more than 8 mU/min if labour was being induced, but that in spontaneous labour sensitivity of the uterus increased, and that if uterine activity had already reached 250 MU, 'even as little as 2 mU/min may be an overdose'. More recently, Seitchik & Castillo (1982), using the same uterine activity criteria, found a 33% hyperstimulation rate in oxytocin augmented labour, and subsequently commented that 'most patients in dysfunctional labour will respond with cervical dilatation to doses of oxytocin of 4 mU/min or less' (Seitchik & Castillo 1983). Hemminki *et al.* (1985) found a 37% hyperstimulation rate in 27 patients where slow labour was augmented with oxytocin, compared with only one in 30 women managed by encouraging ambulation. Finally, Arulkumaran *et al.* (1987) found a 23% incidence of hyperstimulation in a group of primigravidae given an average maximum oxytocin infusion dose of 15mU/min for induction of labour. In the light of these published findings, we can only assume that the statement that at the National Maternity Hospital 'in 3181 primigravidae receiving (high dose, up to 40 mU/min) oxytocin . . . there was no case of hyperstimulation' reflects the fact that in that institution objective measurement of uterine activity using intrauterine catheters is seldom, if ever, used. As regards the practical value of cardiotocographic monitoring of uterine activity, a good example originates from Dr Stronge's own hospital. In response to the observation that in the Dublin trial of fetal monitoring (MacDonald *et al.* 1985*a*) 70% of babies having neonatal convulsions had mothers who had been given oxytocin, compared with only 23% of the total population, Dr MacDonald has written 'it is very plausible that some of the protective effect of electronic fetal monitoring was against "oxytocin induced asphyxia" ' (MacDonald *et al.* 1985*b*).

Ken Bidgood
Phil Steer
Department of Obstetrics and Gynaecology
St Mary's Hospital Medical School (Mint Wing)
Praed Street
London W2 1PG

References

Arulkumaran, S., Ingemarsson, I & Ratnam, S S (1987) Oxytocin titration to achieve preset active contraction area values does not improve the outcome of induced labour. *Br J Obstet Gynaecol* **94,** 242-248

Caldeyro-Barcia, R., Sica-Blanco, Y , Poseiro, J. J., Gonzalez-Panizza, V., Mendez-Bauer, C , Fielitz, C., Alvarez, H , Pose, S. V & Hendricks, C H (1957) A quantitative study of the action of synthetic oxytocin on the pregnant human uterus. *J Pharmacol* **121,** 18-31.

Hemminki, E., Lenck, M., Saariksoki, S. & Henriksson, L. (1985) Ambulation versus oxytocin in protracted labour. a pilot study *Eur J Obstet Gynecol Reprod Biol* **20,** 199-208

MacDonald, D., Grant, A., Sheridan-Pereira, M , Boylan, P. & Chalmers, I (1985*a*) The Dublin randomized controlled trial of intrapartum fetal heart rate monitoring *Am J Obstet Gynecol* **152,** 524-539.

MacDonald, D., Sheridan-Pereira, M., Boylan, P., Grant, A. & Chalmers, I. (1985*b*) Is oxytocin the culprit?—Reply. *Am J Obstet Gynecol* **153,** 929.

Poseiro, J J. & Noriega-Guerra, L. (1961) Dose response relationships in uterine effects of oxytocin infusions. In *Oxytocin* (Caldeyro-Barcia, R & Heller, H., eds), Pergamon Press, Oxford.

Seitchik, J & Castillo, M. (1982) Oxytocin augmentation of dysfunctional labor. I. Clinical data. *Am J Obstet Gynecol* **144,** 899-905.

Seitchik, J. & Castillo, M (1983) Oxytocin augmentation of dysfunctional labor. II Uterine activity data. *Am J Obstet Gynecol* **145,** 526-529.

Steer, P J., Carter, M. C., Gordon, A J & Beard, R W. (1978) The use of catheter-tip pressure transducers for the measurement of intrauterine pressure in labour. *Br J Obstet Gynaecol* **85,** 561-566

British Journal of Obstetrics and Gynaecology
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BOOK REVIEWS

Pathology of the Vulva and Vagina (Contemporary Issues in Surgical Pathology, Vol. 19) edited by E J. Wilkinson. Churchill Livingstone, Edinburgh, 1987, 340 pages with figures and tables, £45.00

This is a well-produced, extensively referenced, authoritative text written by a team of experienced American pathologists and gynaecologists many of whom have published extensively on their chosen topics. It is particularly strong in the way in which it handles current conceptual and diagnostic problems.

Although the book is not intended to be a comprehensive review, there are curious omissions, for example, malignant lesions of the vagina are described in some detail but benign neoplasms, with the exception of condylomata, are omitted.

It is to be regretted that although one author manages to include the 1986 ISSVD recommendations on the terminology of vulval epithelial disorders, the section on 'vulval dystrophies' uses the 1976 nomenclature which has been superseded.

The section on vulval intraepithelial neoplasia uses the preferred VIN terminology but that on vaginal intraepithelial neoplasia, whilst mentioning VAIN perpetuates the terms dysplasia and carcinoma *in situ* in reference to both the vaginal and associated cervical lesions, a classification which has, to great advantage, been replaced by terms which emphasize the concept of a continuum of intraepithelial neoplasias of varying degrees of differentiation. These anachronisms have no place in a book which will undoubtedly be used by gynaecologists and pathologists in training, as well as experienced colleagues, and which includes such excellent up-to-date reviews as those on condylomata and vulval intraepithelial neoplasia.

With such exceptions, however, the book fulfills the editor's intention of addressing those ideas and diagnostic problems in the forefront of this area of pathology and is easy to read, well-illustrated and will prove useful to gynaecologists and pathologists alike.

C. Hilary Buckley

New Developments in Imaging edited by Rainer Ch. Otto & Charles B. Higgins. Georg Thieme Verlag, Stuttgart, New York, 1986, 172 pages with figures and tables, DM98

The contents of this book are based on the papers presented during a satellite 'tele'conference' which took place between a group in the USA and one in Zurich in December 1985. The book, however, is not merely a transcript of the papers but comprises 15 chapters reviewing the papers presented in the relevant sessions of the conference. Each chapter takes the form of an authoritative review paper based not only on the material presented during the conference but on a review of the world literature and the personal opinion and experience of the authors of each section.

The resulting book is much more readable, informative and valuable than the more common 'proceedings' so often published after such meetings. Regrettably the gestation period for production of such a book is much greater than for simple proceedings and in this case appears to have been nearly a year. Of all the fields of modern medicine, medical imaging is progressing most rapidly at the moment and several of the fields discussed in this book, especially magnetic resonance imaging, have advanced significantly during the time interval since the conception of this book. As a result of this delay the quality of many of the images presented is markedly inferior to the current state of the art. In practice this detracts little from the value of the book which derives mostly from its succinct and readily understandable presentation of the indications for the modern imaging techniques and reviews of their clinical applications.

The first five chapters discuss various aspects of magnetic resonance imaging, the subsequent two discuss cine computed tomography and the remaining chapters cover the applications of diagnostic ultrasound. In general the presentations are very clinically orientated though some include technical details of the imaging systems, these are more or less understandable to the clinician. Perhaps of greatest interest to the obstetrician and gynaecologist is the apparent utility of MRI imaging in the management of carcinoma of the uterine body and cervix and in the assessment of other female pelvic pathologies and physiological changes. The authors have convinced themselves that MRI is superior to CT scanning in certain clinical situations and present a fascinating demonstration of the apparent changes within the myometrium during administration of oral contraceptives. The ability of the technique to see 'small pelvic lesions' in the absence of a distended urinary bladder and to produce complete coronal, sagittal or transaxial images would certainly seem to give the technique enormous advantages as a diagnostic imaging procedure. These are currently significantly outweighed by the enormous cost of the investigation.

The chapters on cine CT refer primarily to cardiac and secondarily to liver imaging and are probably of little interest or relevance to the readers of this Journal.

The final eight chapters in the book might be assumed to be of more relevance since they cover the topic of ultrasound diagnosis. However, I must confess to being rather disappointed in both the content and standard of many of these chapters There is very little really new information and the recent major advance of intra-vaginal scanning in obstetrics and gynaecology came too late for inclusion in this book and renders much of the gynaecological content passé.

The book is of considerable interest to those who wish to update their knowledge about magnetic resonance imaging but most obstetricians and gynaecologists will learn little new or relevant from the remainder of the text.

Hylton B. Meire

Clinical Gynecologic Oncology by P. Kolstad. Norwegian University Press (distributed by Oxford University Press), 1987, 247 pages with figures and tables, £29.50

In this day and age it is unusual indeed to see a book of such breadth written by a single author but experience over many years in a centre which recently covered two thirds of the Norwegian population for gynaecological cancer makes this a unique document.

Dr Kolstad covers the entire field from histopathology to diagnosis and management. Although a surgeon by training, he was head of the whole unit from 1967 to 1984 and has a remarkable knowledge of all the areas of which he writes. He draws heavily on publications written by staff from his department and it could be argued that some chapters would have benefited from being presented by colleagues specializing in each field Nevertheless, the single author makes for a uniform approach to each chapter which is clearly written and based almost entirely upon the unit's very wide experience.

Some of the most important chapters deal with the rarer forms of tumour where relatively large numbers have accrued over the years. Examples are: carcinoma of the vulva (445 cases), sarcoma of the uterus (173 cases) and granulosa cell tumour of the ovary (118 cases). The wealth of experience here can only be accumulated elsewhere by means of prospective collaborative trials and no long-term data are yet available.

The format of this book is attractive, the writing is clear and photographs, graphs and tables are always to the point. In some areas, the analysis of data is not as sophisticated as modern methods would allow but this is a relatively minor point.

This book will be a constant reference work for those who treat gynaecological tumours for many years to come and it leads the reader to ask many pertinent questions as to how we may treat patients better in the future.

E. Wiltshaw

Perinatal Care Delivery Systems (Commission of the European Communities Health Services Research Series No. 1) edited by M. Kaminksi, G. Breart, P. Buekens, H. J Huisjes, G. McIlwaine & H. K. Selbmann. Oxford University Press, Oxford, 1987, 308 pages with figures and tables, £30.00

The collected papers forming this volume were presented in 1984 at a European Community workshop on the evaluation of pre-, peri- and postnatal care delivery systems. Disciplines represented include obstetrics, paediatrics, epidemiology, midwifery, sociology and health economics, and countries represented include the UK, France, Belgium, The Federal Republic of Germany, Ireland, Italy, Luxembourg and the Netherlands.

As one would expect with such a variety of authors the chapters vary in their approach and also in quality, but overall they are marked by a critical and rigorous approach to perinatal care delivery systems. The international comparisons demonstrate the remarkable differences in care systems both at an organizational and clinical level, which are in marked contrast with the overall similarity of outcome as measured by perinatal mortality rates.

Perhaps the most useful chapter for most readers will be those evaluating the use of caesarean section, and of the medical, psychological and economic aspects of intensive neonatal care. These have full and useful bibliographies albeit only up to 1984. However, the chapters on medical and non-medical evaluation of prenatal care and of women's attitudes will also be of considerable interest and remain highly topical.

The book is too expensive to recommend to a wide range of readers, but a copy should be on the bookshelves of every obstetric and neonatal department to be used as a model for routine internal evaluation.

Eva Alberman

Management of Ovarian Cancer edited by G. Blackledge & K. K. Chan. Butterworths, London, 1986, 214 pages with figures and tables, £40.00

This is best described as a volume of essays on the management of carcinoma of the ovary Each section, which concentrates on a particular subject, consists of two contributions from different authors, enabling the same topic to be discussed from different points of view. The advantage of this method of presentation is that it allows a more critical assessment of the management of the many unresolved problems in this disease. There is inevitably some repetition and some confluence of views, but there are sufficient differences between each of the two chapters on each individual subject to stimulate ideas on optimal treatment

The contents of this book include a general chapter on the histopathology of ovarian cancer, followed by one highlighting problem areas; for example that of differentiating metastatic carcinoma of the ovary from primary lesions. A chapter on non-invasive techniques for assessing ovarian carcinoma is comprehensive and includes ultrasound, CT scanning, lymphangiography and MRI. This is complemented by one devoted entirely to imaging using monoclonal antibodies, which is still in its infancy Both chapters on second look laparotomy in the management of ovarian carcinomas come to the same conclusion, i.e. that it has no value as a therapeutic tool, little value as a diagnostic tool and it should therefore not be carried out as a routine clinical procedure. The section on chemotherapy discusses fully whether combination chemotherapy gives real survival advantage compared to single agents. According to the British authors, this question remains unanswered but this point of view is not held by the Netherlands Joint Study Group, which is strongly in favour of combination chemotherapy. Arguments still continue as to whether radiotherapy is superior to chemotherapy in patients with minimal residual disease. It is concluded that whole abdominal radiotherapy treatment is effective, but that radiotherapy to the pelvis alone is no longer indicated. Non-epithelial tumours are discussed in detail by both American and English authors. There is no doubt that while chemotherapy has not radically altered the outlook for epithelial ovarian cancer, it has succeeded in radically improving the prognosis for germ cell tumours. Of particular interest is the role of chemotherapy in the management of dysgerminoma in young women in preference to radiotherapy, despite its high radiosensitivity, as fertility is more likely to be preserved in these young women who have a good prognosis. The final chapters are devoted to research and future approaches in the management of ovarian cancer. In particular, there are separate chapters on in-vitro work with clonogenic assays and in-vivo studies using intraperitoneal therapy.

Overall, the book is well presented, clearly printed and very well referenced, with the references from both contributors for the same subject being given at the end of each section rather than at the end of each individual chapter. Surprisingly, there are no illustrations in the pathology section, which would in my opinion have added considerably to the clarity of the written word.

I would recommend this book to oncologists and gynaecologists who are involved in treating carcinoma of the ovary. Firstly, it is of value in providing insights into the dilemmas of treating this tumour at the present time and secondly, it should help clinicians in their own deliberations in deciding how to treat individual patients. It is worth pointing out, however, that a basic knowledge of ovarian carcinoma is desirable, as the reader is expected to be already familiar with, for example, the WHO classification of tumours and the FIGO staging of ovarian carcinomas. I would therefore advise candidates taking higher examinations to familiarize themselves with basic concepts before amplifying their knowledge by reading this book.

H. E. Lambert

Progress in Obstetrics and Gynaecology Vol. 6 edited by John Studd. Churchill Livingstone, Edinburgh, 1987, 442 pages with figures and tables, £19.95

Six years on, is *Progress* satisfactory? The series still has little competition and remains the definitive collection of review articles in our specialty. The foreword to Volume 5 had an ominously valedictory ring but here in Volume 6 the editor is back at his provocative best with a trenchant preface on the value of research in the private sector. The successful format is unaltered, with about a dozen chapters each on obstetrics and gynaecology, and the range of subjects in Volume 6 is characteristically catholic, from computerization of obstetric records to ovarian cancer. Among the unexpected pleasures are a philosophical contribution from Dame Mary Warnock, and a discussion from Singapore on transsexuals. There are high-tech chapters on uterine contractions and fetal blood gases but the main emphasis is practical, with chapters from Nigeria on destructive operations, from Washington USA on postpartum collapse, and from Birmingham on caesarean hysterectomy. This time 16 of the 37 contributors are from abroad, but the English remains fresh and readable—clever editing, I wonder, or an inspired choice of authors? The schedule of publishing an annual series must be frustrating for authors in rapidly advancing fields (only a handful of references in the chapters on ultrasound and IVF are as recent as 1985) but for most of the articles this problem is unimportant. The editor's particular genius lies in inviting—and obtaining—timely contributions which don't date quickly, and I find myself still referring to all the previous volumes in the series. One final grumble: the reviewers quoted on the cover still seem to feel that these books are aimed at Membership candidates. I wish someone would explain to me how the MRCOG, once obtained, magically confers on a specialist the ability to keep up to date for thirty years without ever buying a book.

J. O. Drife

Problems in Obstetric Anaesthesia (Perinatal Practice Vol. 3) edited by Barbara Morgan. John Wiley & Sons, Chichester, 1987, 198 pages with figures and tables, £32.00

This is the third volume in the *Perinatal Practice* series edited by Professors Geoffrey Chamberlain and Forrester Cockburn. The guest editor of this volume is Barbara Morgan, from Queen Charlotte's Maternity Hospital, and all 14 contributors who join her are from UK centres, making it an all-British production. As expected, the contents include problems related to general anaesthesia such as aspiration of gastric contents, failed intubation and awareness, the complications of epidural anaesthesia and the effects on the fetus and neonate of the various drugs which may be used. But not all of the problems addressed are specifically 'anaesthetic'. Indeed some, such as obstetric shock, severe pre-eclampsia and eclampsia and amniotic fluid embolism, might have been considered specifically 'obstetric' problems in the past Now a multidisciplinary approach is needed to deal effectively with these serious complications: not only the anaesthetist but sometimes the haematologist, physician, intensive care specialist and others may have an important contribution to make, as they do in this text.

So, this is not a book written exclusively by, or for, anaesthetists. It will prove useful to front line obstetricians who intend to continue contributing to, and maintaining responsibility for, the management of major obstetric problems in the multidisciplinary approach to perinatal practice. For anaesthetists it is bound to be seen as a welcome and valued supplement to the existing comprehensive obstetric anaesthesia texts.

R. P. Husemeyer

Books received some of which may be reviewed at a later date

Haines & Taylor Obstetrical and Gynaecological Pathology Third edition edited by H. Fox. Churchill Livingstone, Edinburgh, 1987, £195.00. Volume 1: 1–696 pages fully illustrated; volume 2: 697–1331 pages fully illustrated

A Manual of Labour Ward Practice by J. Malcolm Pearce & Shirley A. Steel. John Wiley & Sons, Chichester, 1987, 283 pages with figures and tables, £17.50

Breast Disease (Contemporary Issues in

Obstetrics and Gynecology) edited by Douglas J. Marchant. Churchill Livingstone, Edinburgh, 1987, 168 pages with figures and tables, £32.00

Oxford Reviews of Reproductive Biology Volume 9 edited by J. R. Clarke. Oxford University Press, Oxford, 1987, 504 pages with figures and tables, £50.00

Transvaginal Sonography edited by Ilan E. Timor-Tritsch & Shraga Rottem. Heinemann Medical Books Ltd, 1987, 165 pages illustrated, £29.95

The Clinician's Guide to Sexually Transmitted Diseases edited by Stuart Levin *et al.* Year Book Medical Publishers, Inc., Chicago, 1987, 98 pages with figures and tables, £13.50

The Physiology of the Lower Urinary Tract edited by Michael Torrens & John F. B. Morrison. Springer-Verlag, London, 1987, 355 pages with figures and tables, £89.00

Current Obstetric & Gynecologic Diagnosis & Treatment Sixth edition edited by Martin L. Pernoll & Ralph C. Benson. Appleton & Lange, Norwalk, Connecticut, 1987, 1139 pages with figures and tables, £30.70

Clinical Endocrinology of Calcium Metabolism edited by T. John Martin & Lawrence G. Raisz. Marcel Dekker, Inc., New York, 1987, 410 pages illustrated, $138.00

Human Blastogenesis: Formation of the Extraembryonic Cavities (Bibliotheca Anatomica No. 30) by H. Vogler, Karger, Basel, 1987, 152 pages with figures and tables, £59.10

Psychosexual Training and the Doctor/Patient Relationship edited by R. L. Skrine. Montana Press, Carlisle, 1987, 392 pages, £17.50 (plus £1.50 postage)

Mechanism of Action, Safety and Efficacy of Intrauterine Devices (Report of a WHO Scientific Group, Technical Report Series 753), World Health Organization, Geneva, 1987. 91 pages, Sw Fr 12

Passe et Present de la Chirurgie Radicale en Cancerologie Gynecologique et Mammaire by F. Uyttenbroeck. Masson, Paris, 1987, 548 pages with figures and tables, Fr 450

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Authors are referred to the general statistical guidelines of Altman *et al.* (1983) for advice about the presentation and interpretation of the statistical aspects of their research.

Altman, D. G., Gore, S. M., Gardner, M. J. & Pocock, S. J. (1983) Statistical guidelines for contributors to medical journals. *Br Med J* **286**, 1489–1493.

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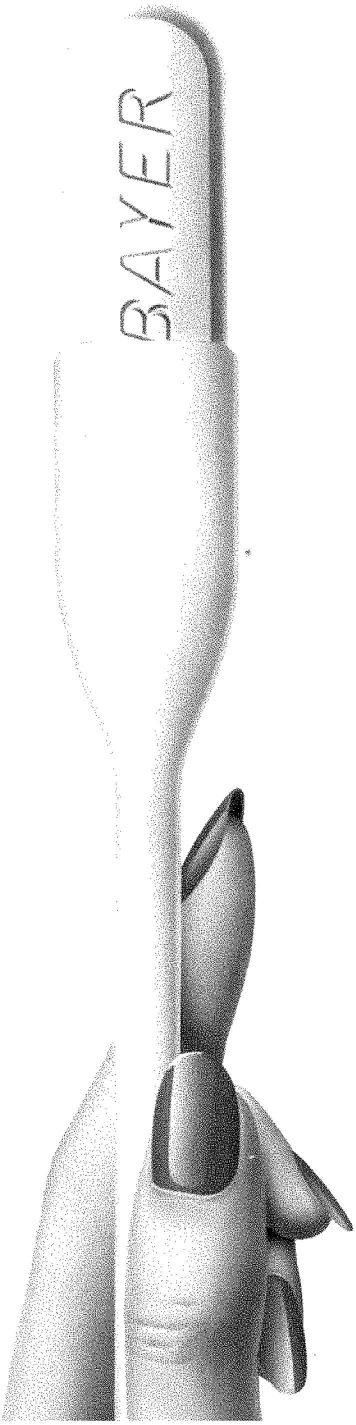

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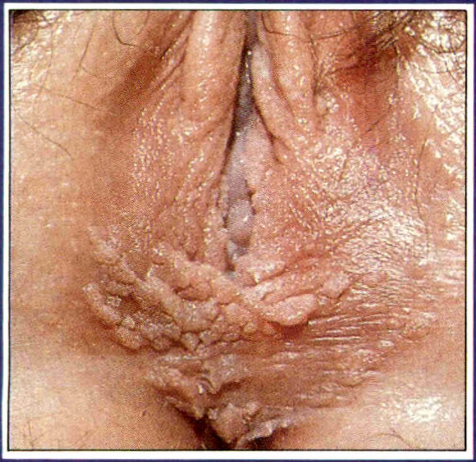

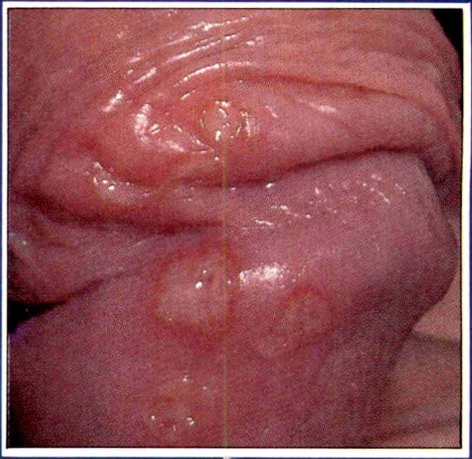

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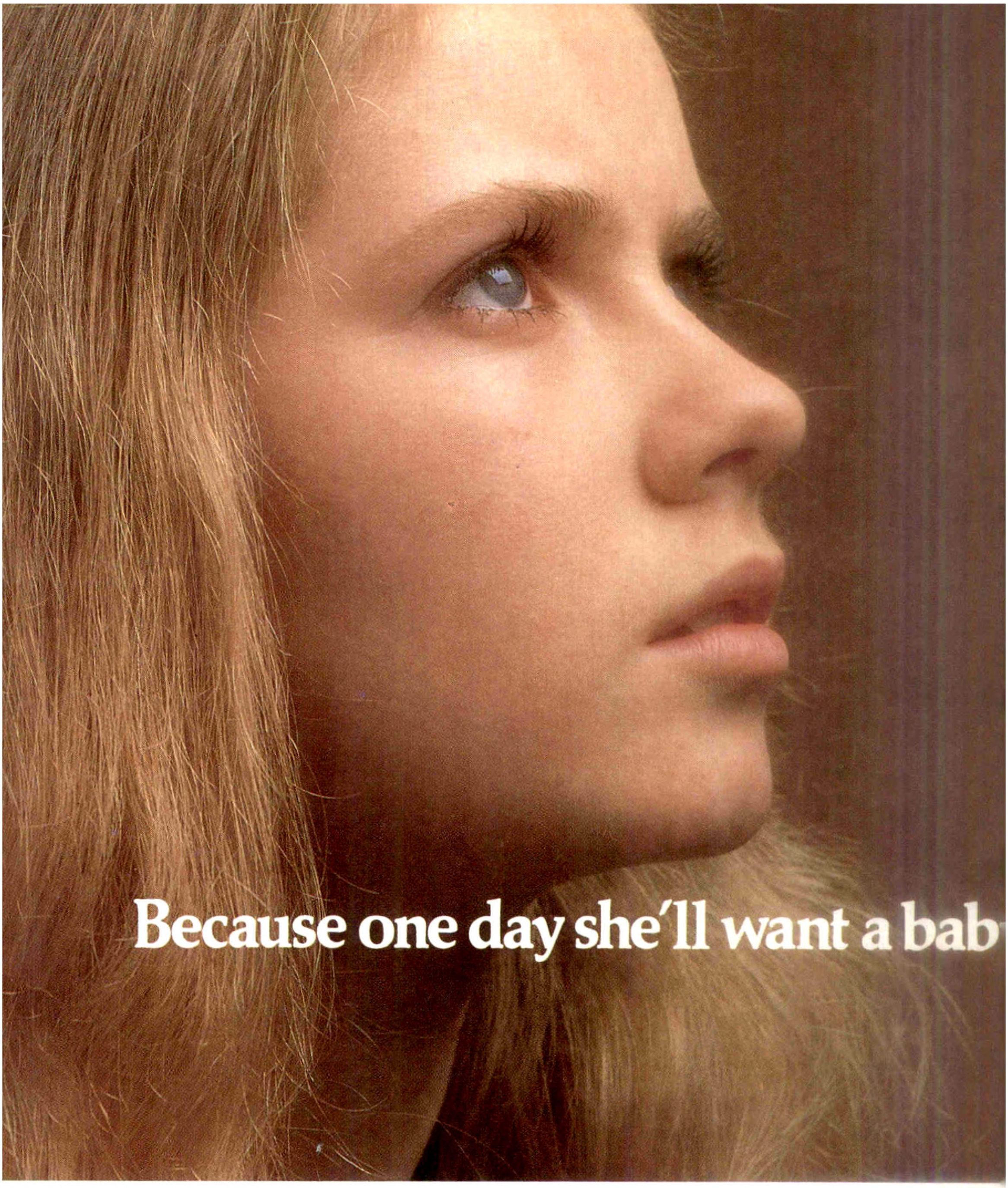
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iit dose foil sachets. **PL No.** 0012/0149. **Basic NHS Cost** (April
6) £82.50 per box. **References:** 1. Harlap,S. *et al.*, *N.Eng.J.Med.*,
9, **301,** 677. 2. Richardson,J.A. & Dixon,G., *Brit.Med.J.*, 1976, **1,**
3. 3. Chen.J.K. & Elder,M.G., *Obstet.Gynecol.*, 1983, **62,** 339.
hristensen,N.J., Bygdeman,M. & Green,K., *Contraception*, 1983,
1), 51. Cervagem is a trade mark. Further information is available
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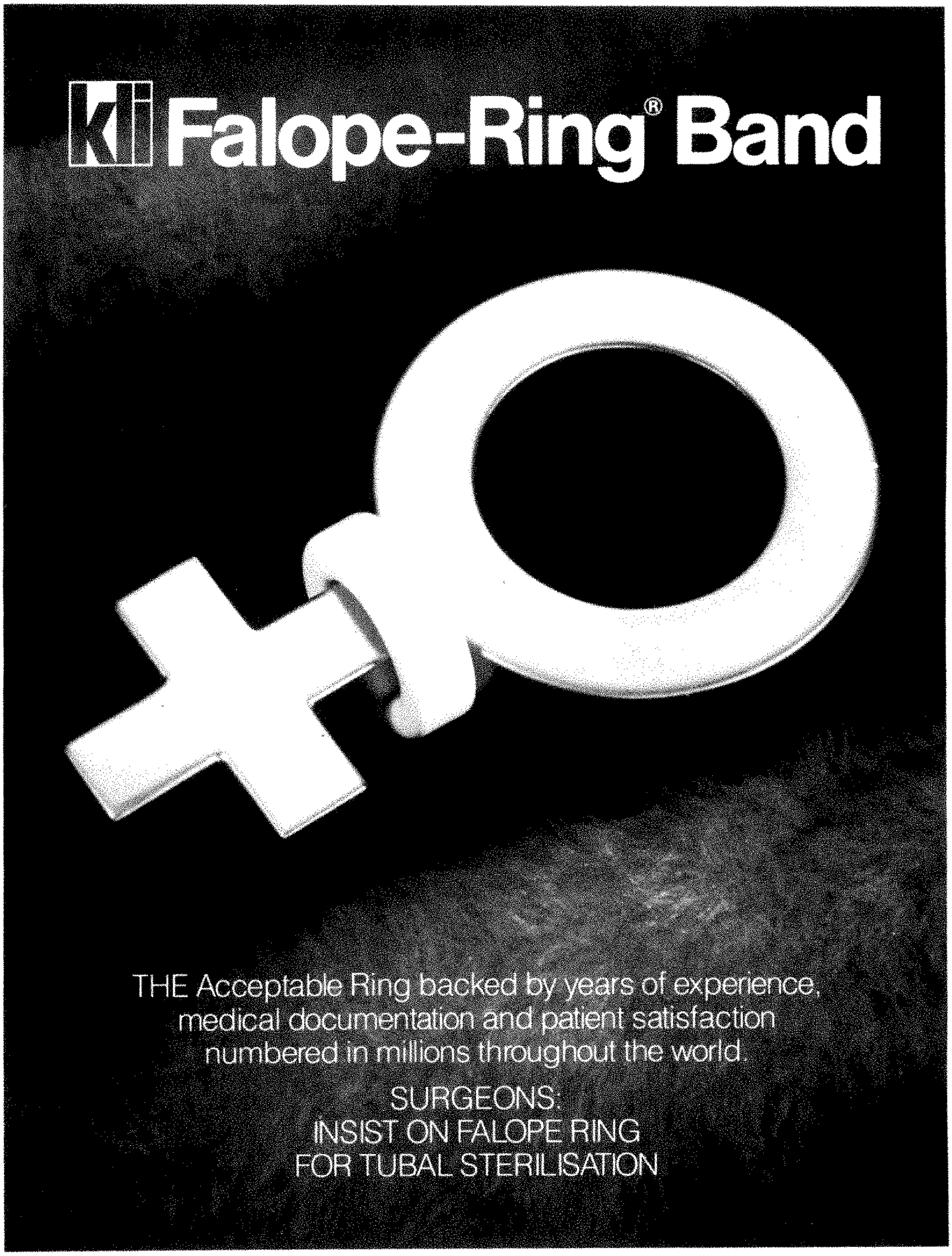

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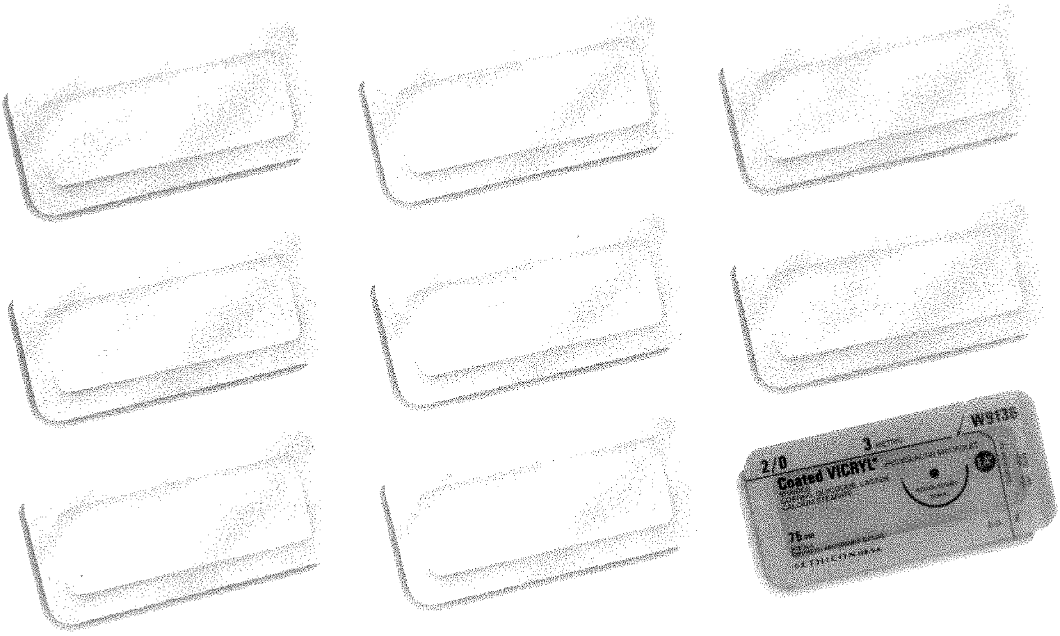

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TECHNICAL DATA

COATED VICRYL* (POLYGLACTIN 910) STERILISED BRAIDED SYNTHETIC ABSORBABLE SUTURE

Presentation The basic VICRYL (Polyglactin 910) Suture is prepared from a copolymer of glycolide and lactide. The substances are derived respectively from glycolic and lactic acids. The empirical formula of the copolymer is $(C_2H_2O_2)m(C_3H_4O_2)n$.

Coated VICRYL (Polyglactin 910) Sutures are obtained by coating the braided suture material with a mixture composed of a copolymer of glycolide and lactide and an equal amount of calcium stearate. This coating does not affect the biological properties of the suture.

Coated VICRYL (Polyglactin 910) Sutures are coloured by adding D & C Violet No 2 during polymerisation of the lactide and glycolide. Sutures may also be manufactured in the undyed form.

These sutures are relatively inert, nonantigenic, nonpyrogenic and elicit only a mild tissue reaction during absorption.

Action: Two important characteristics describe the in vivo behaviour of absorbable sutures. The first of these is tensile strength retention and the second, absorption rate or loss of mass.

Subcutaneous tissue implantation studies of Coated VICRYL Suture in rats show at two weeks post-implantation approximately 55% of its original tensile strength remains, while at three weeks approximately 20% of its original strength is retained.

Intramuscular implantation studies in rats show that the absorption of these sutures is minimal until about the 40th post-implantation day. Absorption is essentially complete between the 60th and 90th days.

Uses Coated VICRYL synthetic absorbable sutures are intended for use where an absorbable suture or ligature is indicated.

Dosage and Administration
By implantation.

Contra-indications, Warnings, etc.
These sutures, being absorbable, should not be used where extended approximation of tissues under stress is required.

Sutures placed in skin and conjunctiva may cause localised irritation if left in place for longer than 7 days and should be removed as indicated.

At the discretion of the surgeon, appropriate non-absorbable sutures may be used to provide additional wound support when Coated VICRYL sutures are used in ophthalmic procedures.

The safety and effectiveness of Coated VICRYL (Polyglactin 910) Sutures in neural tissue and in cardiovascular tissue have not been established.

Pharmaceutical Precautions
Do not re-sterilise.

Legal Category.
Not applicable.

Package Quantities Various lengths of material packaged in sealed aluminium foil sachets. This primary pack is contained in a peel-apart secondary pack. The unit of sale is 12 packs contained in a film wrapped drawer style carton.

Further Information No suture related adverse reactions were reported during clinical trials, although a number of minor reactions were classified as being of unknown cause.

Product Licence No 0508/0009
Br. Pat. No. 1583390

Date of Preparation of Data Sheet April 1981
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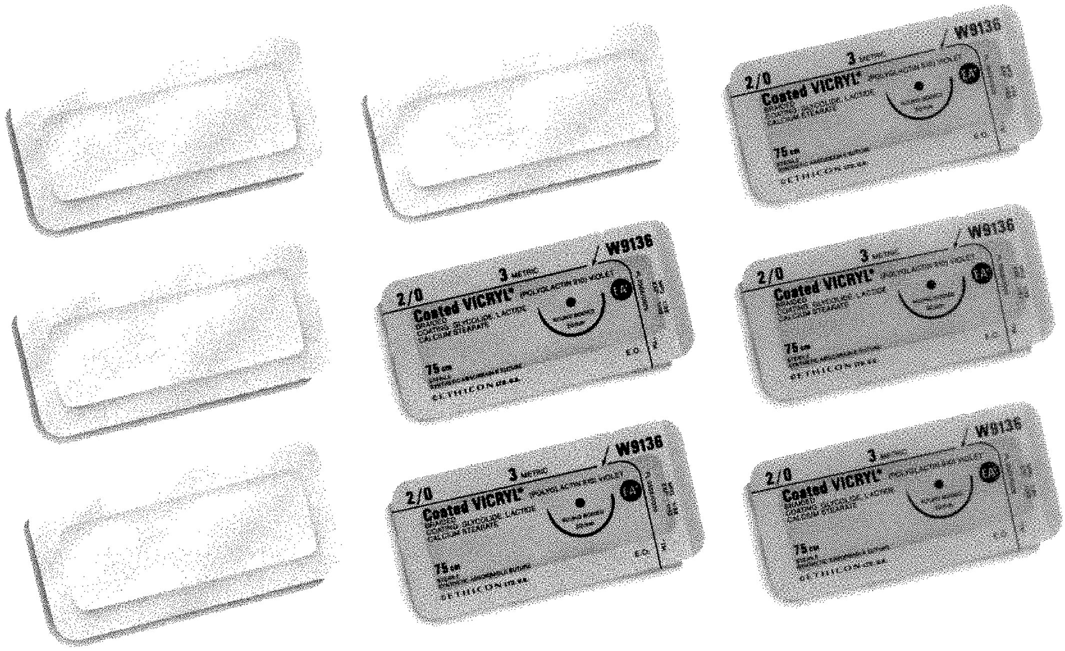

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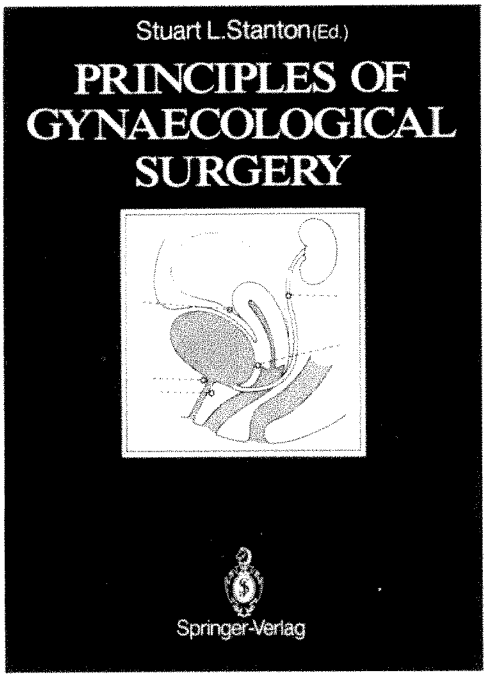

Stuart L.Stanton (Ed.)

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Springer-Verlag

1987. 152 figures. XII, 306 pages.
Hard cover £ 29.50. ISBN 3-540-17485-0

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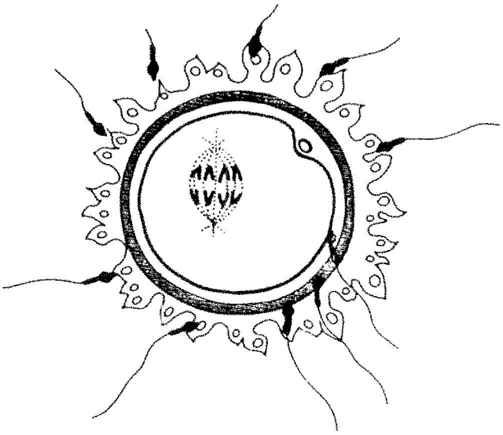

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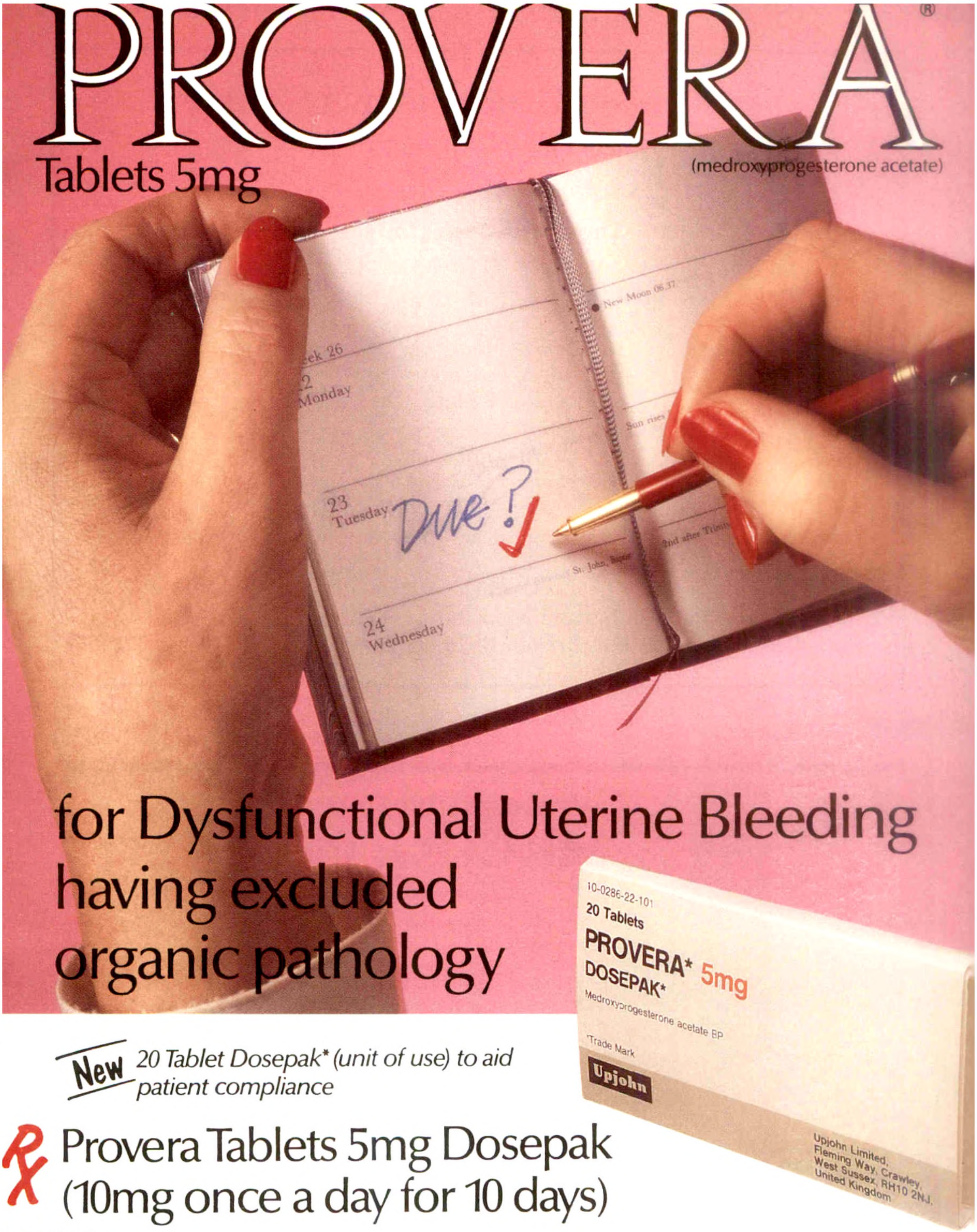

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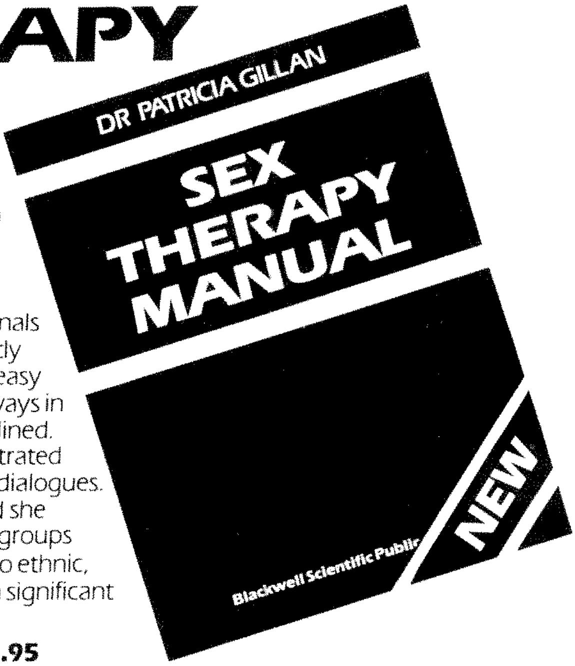

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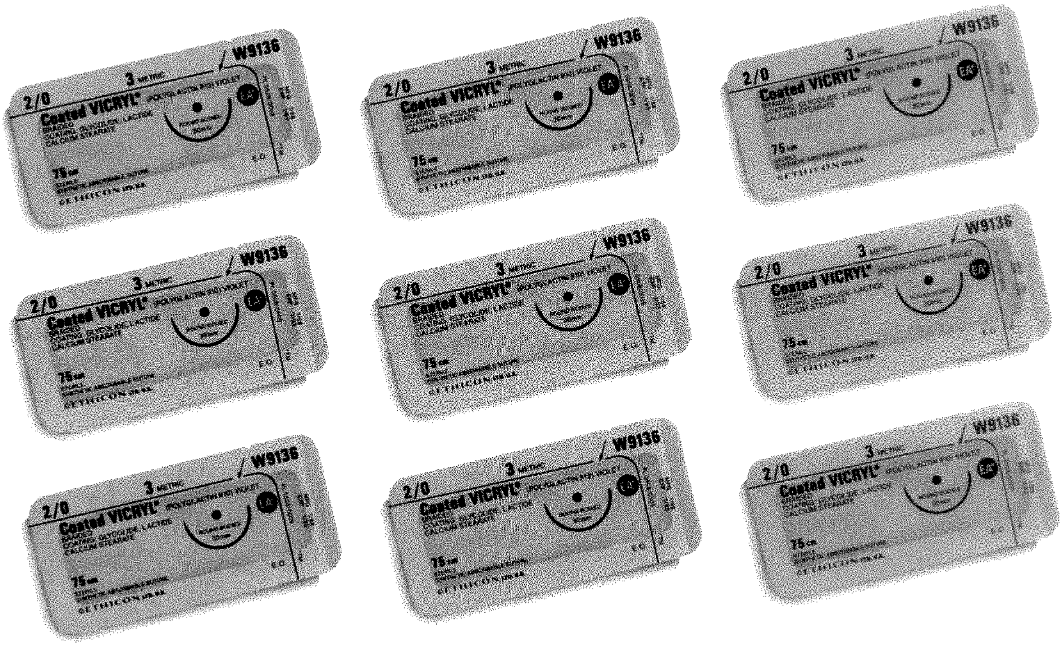

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COMMENTARY

Failed sterilization and the law

The increase in litigation for failure of sterilization continues and recent developments again emphasize that the doctor must be extremely careful with pre-operative counselling and the conduct of the operation. The defence societies have dealt with many claims in recent years and current damages run up to £40 000 per case.

The word sterilization suggests, particularly to the layman, a permanent state of affairs and it is therefore perhaps not surprising that the patient sues when the whole purpose of the operation has failed. Cases of failure attract wide media coverage and most patients are fully aware of the possibility of litigation.

Actions for failed sterilization may allege negligence, trespass to the person or breach of contract. Negligence would be alleged where the operation is performed incorrectly even though the patient has been told about the risk of failure, for instance, where a clip is placed on a round ligament. Trespass would be alleged where the operation fails to sterilize (even though it has been performed correctly) and the patient has not been told about the risk of failure although the courts prefer an action in negligence alleging that the doctor has failed in his duty to inform the patient of the risk of failure (Argent 1985).

In 1983 (Emeh *v.* Kensington, Chelsea & Westminster Health Authority) it was held that pregnancy constitutes an injury where there is a lack of warning about the possibility of failure. The recent case of Gold *v.* Haringey Health Authority (Brahams 1987*a*) attempted to go further and came to some interesting conclusions. In the Queen's Bench Division, Mr Justice Schiemann said that there was a difference between therapeutic and non-therapeutic sterilizations and held that there was a duty to counsel the patient about alternative family planning methods, including vasectomy, when the operation was being done purely to limit family size. However, the judgement was reversed in the Court of Appeal. Lloyd LJ held that there could be no distinction between therapeutic and non-therapeutic treatment and that the Bolam test, that is the standard of the ordinary skilled man, applied. He concluded that to dissect a doctor's advice into that given in a therapeutic context and that given in a contraceptive context would be to go against the whole thrust of the House of Lords' majority decision in a recent case which considered counselling and consent (Brahams 1985). As an aside, Lloyd LJ also said that it remained a matter of surprise that the law acknowledged an entitlement in a mother to claim damages for the blessing of a healthy child.

Both in Gold and another recent case of Cronin *v.* Islington AHA (Brahams 1987*b*), the plaintiffs also failed because at the relevant dates, 1979 and 1981 respectively, it was held that there was a substantial proportion of responsible doctors who would not have warned about a risk of failure. Times change and most doctors now warn of the risk of failure even though, as was revealed during the discussion by the Royal College of Obstetricians and Gynaecologists 14th Study Group (1985) this is by no means universal practice. In Autumn 1984, the Joint Co-ordinating Committee of the Medical Defence Societies, after discussion with the DHSS and at the suggestion of the Medical Defence Union, devised a new consent form, now in wide use, which contains the sentence 'I understand that there is a possibility that I may not become or remain sterile'.

The action in contract failed in Thake *v.* Maurice (1985) (a case of failed vasectomy where the legal principles also apply to female sterilization) where it was held that a surgeon, although not liable in contract, was in breach of his contractual duty by failing to warn of a risk of failure and was accordingly liable in negligence.

It is important to note that if a patient decides to keep a pregnancy after a failed sterilization then her legal action will not usually fail. The legal damage is done and there is no onus on the patient to have an abortion.

It is not usual to discuss the advantages and disadvantages of different operative techniques with the patient, and surgeons are likely to have their own preferences for laparoscopic clip or ring application or diathermy or laparotomy. However, if the patient wishes to discuss different methods or additional potential complications then the surgeon has a duty to use care in answering the patient's inquiry where he knows that she will rely on the answer in deciding whether or not to consent to the proposed treatment. In Blyth *v.* Bloomsbury Health Authority (Brahams 1987*c*), the Court of Appeal held that what a patient should be told in answer to a general inquiry must depend upon the circumstances, the nature of the inquiry, the nature of the information which is available, its reliability, relevance and the condition of the patient.

Caution must be exercised when the sterilization operation is performed at the end of a caesarean section (Barnes 1985). The patient should be told that, for a given method, the failure rate is higher when the operation is performed in this situation. Consent is absolutely essential as the court is very unlikely to consider an unsolicited sterilization necessary for the protection of the patient's life or even the preservation of the patient's health. Consent during labour, especially if the patient is under the effect of drugs, is likely to be no consent at all and pre-operative counselling should take place in normal circumstances several times during a pregnancy. It would be unwise to assume that the patient who consents at the time of booking has not changed her mind in the latter part of pregnancy.

Similar caveats apply to sterilization accompanying abortion operations. Some gynaecologists will not do this as they feel that the patient is making a decision under duress and there is, of course, a higher failure and complication rate which should be discussed. It is common practice to apply two clips to the thickened tubes of early pregnancy.

What can be done to avoid time-consuming litigation? The courts always try to reflect good medical practice and therefore by adhering to certain standards we are, after all, merely providing our patients with the best possible care. We must not forget, however, that the injured patient does have redress if she has suffered through a doctor's negligence. The patient must be told, and the doctor must be sure she understands, that there is a risk of failure. She must be advised to report subsequent amenorrhoea or symptoms of pregnancy. Some gynaecologists add that if the operation fails, then an abortion may be possible if the conditions of the Abortion Act are fulfilled. It would be prudent to warn of the higher risk of ectopic pregnancy even though the courts have not yet required this. The patient should be advised to continue with satisfactory contraception until the operation is performed. Some gynaecologists will not perform these operations in the second half of the cycle where the patient is taking inadequate contraceptive measures. The occurrence of the so-called luteal phase pregnancy can probably be minimized by currettage at the time of the sterilization although if the intent is to procure an abortion then this may constitute a criminal offence unless the terms of the Abortion Act are complied with. When the patient has been advised of the risk of failure, she is asked to sign the specially designed consent form, and the case records should state that the implications of the operation and the risk of failure have been explained. It would be more sensible for the form to be signed after consultation with a senior member of staff who is able to counsel wisely and give proper answers to the patient's questions. The patient should not be rushed. In a recent case of failed sterilization (Jones *v.* Berkshire Health Authority) (Brahams 1986) there was a conflict of evidence as to whether a warning of failure had been given on three different occasions by three different doctors and there was heavy criticism of the clinic 'conveyor belt' system allowing each patient only 6 minutes with the doctor. Consultants must teach their junior staff about the importance of pre-operative counselling.

Obviously failure can be minimized by improvements in technique. Some may prefer to go back to older methods, such as Irving's technique, with their lower failure rate but the patient should be warned of the greater morbidity and difficulty of future reversal. Others will strive to improve newer techniques. We must keep aware of new developments in practice. If there is any difficulty with laparoscopic visualization it is preferable to perform a laparotomy and patients with obesity or pelvic adhesions should be warned of this in advance. If a clip or ring is applied to the round ligament then *res ipsa loquitur* nearly always applies; in the courts, there will be no excuse for departure from our normal high standards. If the application is uncertain, the patient should be informed and she should be offered a postoperative hysterosalpingogram.

Laparoscopic sterilization should only be performed by those with thorough training in the method and junior staff should be carefully supervised by their seniors, preferably with the help of a teaching aid.

With the current trends in litigation, I believe the approach to counselling should be improved and the operation be renamed. The word *sterilization* suggests a permanence that cannot be guaranteed. Sterilization is the intent of the operation and it would be better to describe what we actually do, for instance tubal ligation and excision or laparoscopic application of clips to the fallopian tubes. Very few women sue for failure of the intrauterine device or the contraceptive pill because they realize that these methods are not foolproof. We have a duty to educate the public that these operations are merely more lasting methods of contraception which are difficult to reverse.

Vincent Argent
Consultant Obstetrician and Gynaecologist
District General Hospital
Kings Drive
Eastbourne, East Sussex BN21 2UD

References

Argent, V P. (1985) Failed female sterilization and the law. *Med Sci Law* **25**, 136-142.

Barnes, J. (1985) Failed sterilization. medico-legal aspects. *J Med Defence Union* **1** **(no. 2)**, 9-10

Brahams, D. (1985) Doctor's duty to inform patient of substantial or special risk when offering treatment. *Lancet* **i**, 528-530

Brahams, D. (1986) Court not bound to accept test of competent medical practice in deciding whether contraceptive counselling is negligent. *Lancet* **ii**, 407-408

Brahams, D. (1987*a*) Doctor's duty of care to give advice in therapeutic and non-therapeutic contexts. *Lancet* **i**, 1045.

Brahams, D. (1987*b*) Pregnancy following sterilization: two cases fail. *Lancet* **i**, 638

Brahams, D. (1987*c*) Doctor's duty to answer patients' inquiries. *Lancet* **i**, 932.

Emeh *v*. Kensington, Chelsea & Westminster Health Authority (1983) *The Times*, 3 January

RCOG 14th Study Group (1985) *Litigation and Obstetrics and Gynaecology. Proceedings of the Fourteenth Study Group* (Chamberlain, G. V. P , Orr, C. J. R & Sharp, F., eds), RCOG, London, pp. 163-192.

Thake *v*. Maurice (1985) *The Times*, 16 December.

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Comparison of pregnancy-specific β_1-glycoprotein (SP_1) and ultrasound in predicting the date of delivery

A. NAIEM, N. A. BERSINGER, P. J. KELLER, H. SCHNEIDER

Summary. The accuracy of ultrasound measurements (crown–rump length and gestational sac diameter) and the serum concentration of pregnancy-specific β_1-glycoprotein (SP_1) in the prediction of the date of birth was analysed in a study population of 94 patients. When measured before 8 weeks after the last menstrual period (LMP) the serum concentration of SP_1 was found to be a good predictor of the expected date of delivery and a good alternative to ultrasound, but it was of limited use when determined at a later gestation.

The accurate assessment of gestational age is the basis for optimal antenatal care and of great clinical importance. The reliability of menstrual dates and clinical variables is limited and may be misleading (Robinson 1973). The traditional method relies on the menstrual dates as stated by the patient, with confirmation by abdominal or vaginal examination. Confirmation by more precise measurements is desirable especially when the date of the last menstrual period (LMP) is uncertain or when the menstrual cycle was irregular. Another way of determining the gestational age is an early ultrasound examination. Crown-rump length (CRL) measured before 12 weeks gestation is one of the most precise sonographic methods to determine gestational age (Robinson & Fleming 1975; Drumm *et al.* 1976).

Recently it has been claimed that determination of pregnancy-specific β_1-glycoprotein (SP_1), a member of the new generation of placental proteins (Bohn 1972), was at least as accurate as the LMP or ultrasound (Ahmed & Klopper 1985). The purpose of the present study was to reassess the value of SP_1 determinations compared with the performance of ultrasonographic methods, in predicting the date of delivery.

Patients and methods

The study population consisted of women attending the antenatal clinic of the University Hospital of Zurich. Singleton pregnancies at between 5 and 16 weeks from LMP were selected and closely supervised for absence of any pathology in pregnancy, labour, or parturition. The study criteria of uneventful pregnancy, spontaneous labour later than 37 weeks from LMP, and birth of a normal baby were fulfilled in 94 patients who remained for the final analysis. In seven patients ovulation had been induced with clomiphene and embryo transfer was performed in one.

Ultrasound measurements of gestational sac diameter (GS) or CRL used a Toshiba Sonolayer-L SAL-35A apparatus at a frequency of 3·5 MHz. A blood specimen was taken and the serum stored at −25°C before SP_1 assay. These determinations were performed in batch using the radioimmunoassay provided by Behringwerke (Riagnost-SP_1). When the standard assay protocol was followed, the range of this method was 5·5–400 ng/ml. Sera showing

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Department of Obstetrics and Gynaecology, University Hospital of Zurich, Switzerland
A NAIEM
N. A. BERSINGER
P. J KELLER
H. SCHNEIDER*

Correspondence: Dr N. A Bersinger, Department of Obstetrics and Gynaecology, University Hospital, 8091, Zurich, Switzerland

* Present address: Universitats-Frauenklinik, Schanzeneckstrasse 1, 3012, Bern, Switzerland

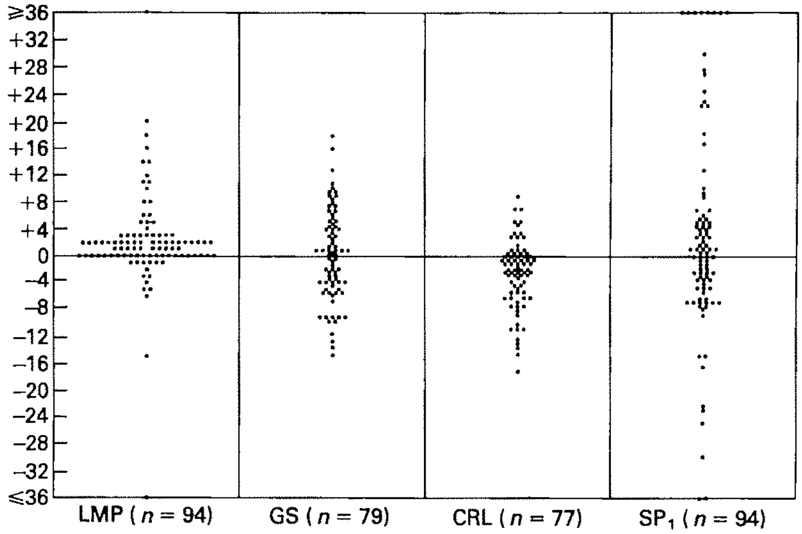

Fig. 1. The difference (in days) between the date of birth (DOB) as calculated from LMP, GS, CRL and SP_1 minus the true DOB, in the interval up to 16 weeks.

values above 400 ng/ml were diluted with male serum or albumin buffer and assayed again using the same method. Sera with values below 5·5 ng/ml were retested with the more sensitive enzyme immunoassay first described by Grenner (1978) and marketed by the same company (Enzygnost-SP_1). This sandwich-type immunometric assay had a sensitivity of 0·5 ng/ml. Internal quality control samples at various concentrations of SP_1 yielded identical results with both immunoassays involved.

The prediction of the date of birth (DOB) was obtained (i) from the menstrual dates, DOB = LMP + 280 days; (ii) from the GS measurement using the formula GS diameter (in cm) = 0·537 × weeks − 1·401 (Reinold 1976); (iii) from the CRL measurement with the uncorrected formula described by Robinson & Fleming (1975), gestation = 8·052 × $\sqrt{CRL}$ + 23·73 (CRL expressed in mm); and (iv) from the SP_1 concentration as described by Ahmed & Klopper (1985) using the following equations: gestation (days from LMP) = 39·71 + 0·0026 × SP_1 (expressed in ng/ml) when the SP_1 value was above 75 ng/ml (in the original paper µg/ml was incorrectly used for ng/ml). For the lower readings the other equation was used: gestation = 28·82 + 0·089 × SP_1.

For ultrasound measurements and SP_1 (ii–iv) the expected date of birth was calculated from the gestational age (as obtained by the above quoted formulas) using a computer program. The dates were later compared with the true DOB and the difference (in days) was established.

Results

For each variable (LMP, GS, CRL and SP_1) and each patient the difference between the calculated date of birth and the true date of birth (in days) was determined. These data are shown in Fig. 1. It can be seen that the ultrasound measurement of CRL was consistent with a slight underestimation, while dating based on LMP seemed to be positively skewed. SP_1 results were spread out over a wide range and rendered this test less accurate for predicting the DOB. The extremes of deviation were −66 and +224 days. Table 1A illustrates this observation further with percentages shown for weekly intervals. Only 72·3% of all DOB predictions obtained from SP_1 were found to fall within ± 2 weeks of the actual DOB, while these values were 96·2% for GS, 97·4% for CRL, and 94·6% for LMP.

When the analysis was restricted to the measurements obtained up to and including week 8 of pregnancy (DOB minus 224 days), the DOB prediction by SP_1 was as good as by CRL (100% within ± 2 weeks, Table 1B, Fig. 2).

Table 2 gives the means and standard deviations of the above differences obtained with the four predictors calculated for the two gestational age groups (≤8 weeks and ≤16 weeks). The means are tabulated to illustrate the skewness,

Table 1. Per cent distribution of date of birth (DOB) predictions as calculated from LMP, GS, CRL and SP_1 with respect to the true DOB, measured in pregnancies (A) up to 16 weeks and (B) up to 8 weeks gestation

	Per cent DOB predictions by difference from true DOB (days)				
	Underestimate		Within	Overestimate	
Predictor	>14	14	± 7	14	>14
(A) ≤16 weeks gestation					
LMP	1·1	0	86·1	8·5	4·3
GS	1·3	12·7	69·6	13·9	2·5
CRL	2·6	15·6	79·2	2·6	0
SP_1	9·6	4·3	61·6	6·4	18·1
(B) ≤8 weeks gestation					
LMP	2·0	0	88 2	5·9	3·9
GS	2·2	15·2	67·4	10·9	4·3
CRL	0	8·3	86·4	5·6	0
SP_1	0	3·9	90·2	5·9	0

LMP, Last menstrual period; GS, gestational sac diameter; CRL, crown–rump length, SP_1, pregnancy-specific β_1-glycoprotein.

and the SD values are themselves an indicator for the accuracy of DOB prediction. Predictions from LMP and ultrasound are not greatly affected by the gestational age at the time of measuring: the SD values are not improved in the analysis restricted to data obtained before 8 weeks. SP_1 was a very good predictor in this restricted group of patients; the mean was closer to zero and the SD was smaller than the findings for LMP, GS or CRL. However, above 8 weeks gestation, SP_1 lost all its potency as a DOB predictor, with a strong positive skewness and a huge SD due to extreme values.

Discussion

The gestational age is normally established by the date of the LMP and clinical examination (size of the uterus). More recently, ultrasound measurements as well as hormone determinations have been added. By examining selected patients whose gestational ages are known precisely, the correlations between the ultrasonically measured growth of CRL or gestational sac or between the rise in serum concentration of various hormones on the one hand, and gestational age on the other were determined.

With all methods that are used to estimate fetal age the biological variation increases with advancing gestational age. Therefore the measurements made close to fertilization should be most reliable (Drumm *et al.* 1976). Currently a variety of tests are undertaken in early pregnancy, using ultrasound (GS, CRL) or hormone assays. Lagrew *et al.* (1983) used human chorionic gonadotrophin (hCG); Whittaker *et al.* (1983) measured human placental lactogen (hPL), and Ahmed & Klopper (1985) determined SP_1.

Although the exact knowledge of the gestational age is of great value to the clinician one

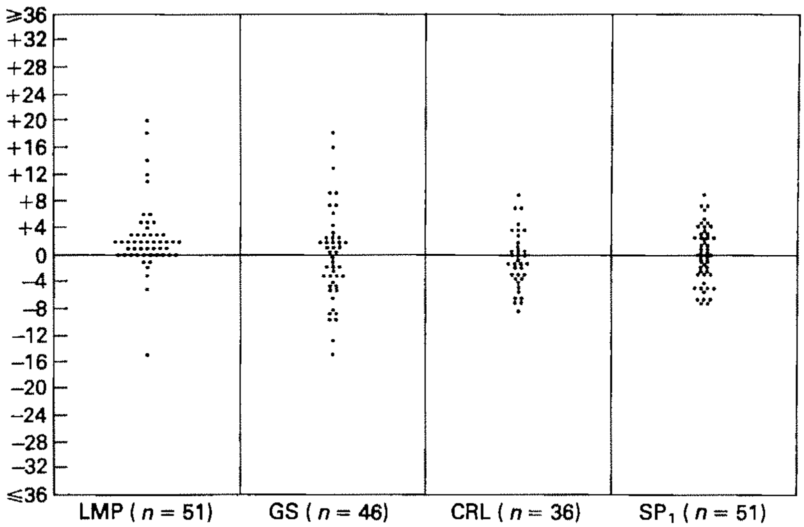

Fig. 2. The difference (in days) between the date of birth (DOB) as calculated from LMP, GS, CRL and SP_1 minus the true DOB, in the interval up to 8 weeks.

Table 2. Mean and SD of the differences between date of birth (DOB) as calculated from LMP, GS, CRL and SP_1 estimations at ≤8 weeks and ≤16 weeks gestation and the actual DOB

	Difference from true DOB (days)			
	Up to 8 weeks		Up to 16 weeks	
Source of calculated DOB	Mean	SD	Mean	SD
LMP	2·39	5·34	2·05	7·40
GS	−0·43	7·07	−0·36	6·88
CRL	−0·60	4·17	−2·93	5·17
SP_1	0·21	4·09	8·04	34·56

LMP, Last menstrual period; GS, gestational sac diameter; CRL, crown–rump length; SP_1, pregnancy-specific β_1-glycoprotein.

must keep in mind that the length of pregnancy and growth and development of the fetus under normal conditions is subject to considerable biological variation. It was therefore interesting to examine in a normal clinic population how accurately the date of delivery could be predicted by LMP, ultrasound, or SP_1 measurements in early pregnancy. In a first part the total group was analysed and in a second part those patients who had registered before 8 weeks were separately assessed. With LMP and ultrasound a high degree of accuracy was achieved for the whole group of patients while the prediction with SP_1 was less accurate. Close to 20% of normal deliveries occurred more than 14 days after and almost 10% more than 14 days before the predicted date. The clinical implication of such poor prediction could be either unnecessary induction of labour or unnecessary prevention of preterm labour. LMP and both ultrasound measures were clearly superior. It is interesting that LMP tended to overestimate the expected date of delivery with a predominantly positive difference between the calculated date and the actual date of delivery. CRL on the other hand tended to underestimate the actual date of delivery. We have no good explanation for this finding.

When the analysis was restricted to the data from pregnancies obtained before 8 weeks, SP_1 was at least as accurate in predicting the DOB as the other measures. All deliveries took place within ± 7 days of the calculated DOB, and there was no evident over- or underestimation. Our findings with SP_1 in this subgroup are in good agreement with the results published by Ahmed & Klopper (1985), whereas in pregnancies up to 16 weeks, SP_1 determinations were less accurate in predicting the DOB than was reported by Ahmed & Klopper (1985).

In conclusion, we consider that in pregnancies less than 8 weeks from the LMP, the DOB can be predicted by SP_1 measurements as a good alternative to ultrasound and may even be preferable since physical exposure of the embryo to ultrasound is prevented during a most sensitive stage of development. However, in all pregnancies with SP_1 values of >300 ng/ml, an ultrasound examination is required to obtain accurate dating and to detect multiple gestations.

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References

Ahmed, A. G. & Klopper, A (1985) Observations on the dating of pregnancy. *Eur J Obstet Gynaecol Reprod Biol* **20,** 347-355

Bohn, H. (1972) Isolierung und Charakterisierung des schwangerschaftsspezifischen β_1-Glycoproteins *Blut* **24,** 292-302.

Drumm, J. E., Clinch, J & MacKenzie, G. (1976) The ultrasonic measurement of fetal crown–rump length as a method of assessing gestational age *Br J Obstet Gynaecol* **83,** 417-421.

Grenner, G. (1978) Enzymimmunoassay zur Bestimmung des schwangerschaftsspezifischen β_1-Glycoproteins (SP_1). *Fresenius Z Anal Chem* **290,** 99.

Lagrew, D. C., Wilson, E A. & Jawad, M. J. (1983) Determination of gestational age by serum concentrations of human chorionic gonadotrophin. *Obstet Gynecol* **61,** 37-40.

Reinold, E. (1976) Ultrasonics in early pregnancy *Contrib Gynecol Obstet,* Vol 1, Karger, Basel.

Robinson, H P. (1973) Sonar measurement of fetal crown–rump length as means of assessing maturity in first trimester of pregnancy. *Br Med J* **iv,** 28-31.

Robinson, H. P. & Fleming, J. E. (1975) A critical evaluation of sonar crown–rump length measurements. *Br J Obstet Gynaecol* **82,** 702-710.

Whittaker, P. C., Aspillaga, M. O & Lind, T (1983) Accurate assessment of early gestational age in normal and diabetic women by serum human placental lactogen concentrations. *Lancet* **ii,** 304-306.

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Magnesium supplementation in pregnancy. A double-blind study

LUDWIG SPÄTLING, GABRIELE SPÄTLING

Summary. The effect of magnesium supplementation in pregnancy was studied in 568 women who were treated with 15 mmol magnesium-aspartate-hydrochloride per day or aspartic acid as placebo given orally during pregnancy from ≤16 weeks. Allocation to the two groups was performed according to the women's birthdates. Magnesium supplementation during pregnancy was associated with significantly fewer maternal hospitalizations, a reduction in preterm delivery, and less frequent referral of the newborn to the neonatal intensive care unit. The results suggest that magnesium supplementation during pregnancy has a significant influence on fetal and maternal morbidity both before and after delivery.

In recent years, although intensive care has resulted in an important increase in neonatal survival rates, preterm delivery remains responsible for most neonatal morbidity. Even though magnesium has had its place in obstetrics for the management of eclampsia since the beginning of the century, a connection with preterm labour was only recognized in the 1960s (Dumont 1965). Wider interest in the role of magnesium in obstetrics was reactivated by our observations that supplemental magnesium medication allowed a considerable reduction in the dose of beta adrenergic agents used for tocolysis of preterm labour (Spatling 1981). Based on these findings, Conradt *et al.* (1984) showed in a retrospective study that the frequency of fetal growth retardation and pre-eclampsia was reduced in association with magnesium supplementation. In the light of these findings, we conducted a double-blind study to clarify whether magnesium supplementation has an influence on these variables. The following null hypotheses were stated: magnesium supplementation has no effect on: (i) pre-eclampsia; (ii) preterm labour (and consequently gestational age at delivery) and (iii) fetal growth.

Subjects and methods

Between March 1983 and March 1985 all patients who attended the outpatient clinic at the department of obstetrics, University of Zürich, were asked to participate in the study. All normal- and high-risk patients were included. A total of 568 women gave their general agreement and they were included in the trial as early as possible in pregnancy, but not later than 16 weeks gestation which was estimated from the first day of the last menstrual period. This sample size was determined by the limitation of the recruitment period which, for practical reasons, could not exceed 2 years.

The method of allocation was based on the subjects' date of birth. Women with an even birthdate were given 15 mmol of magnesium-aspartate-hydrochloride; women with an odd birthdate were given a placebo containing 13·5 mmol of aspartic acid per day. These doses were divided into six tablets to be taken daily. At

Department of Obstetrics, University of Zurich, Switzerland
LUDWIG SPATLING

Research Unit, Department of Obstetrics and Gynecology, University of Bochum, Marienhospital Herne, Federal Republic of Germany
GABRIELE SPATLING

Correspondence. Dr Ludwig Spatling, Universitats-Frauenklinik Bochum, Marienhospital, Holkeskampring 40, D 4690 Herne 1, FRG

each visit patients were questioned on regular intake, number of tablets and side-effects of medication.

Classification of diagnoses and therapies used the coding system of the Munich Perinatal Study (Selbmann *et al.* 1980).

Statistical analysis

The Wilcoxon and Mann–Whitney *U*-tests were used to compare the central trends. Categorical variables were analysed by the χ^2 test. The results were considered significant at the 5% level. Assessment always used two-tailed tests. Values are given as medians and the 5th and 95th centiles. For various reasons, such as refusal to take further tablets, delivery in other hospitals or abortion, some data were not available for analysis. Reference values for the 10th centile of birthweight were taken from Largo *et al.* (1980).

Results

Of the 568 women entered into the study, 278 were treated with magnesium and 290 received the placebo. Age, parity and gravidity were similar in the two groups. There was no difference with regard to the birthweight of children born before the start of this study or the duration of previous pregnancies (Table 1). Based on the clinical history of the patients, the risk of abnormal pregnancy was comparable in the two groups.

The daily rate of tablet consumption was comparable in the two groups. However, the total number of tablets ingested was much higher in the group receiving magnesium, because of the longer length of gestation in that group (Table 2).

The frequency of complaints attributed to the tablets was low and comparable in the two groups. In the magnesium group one woman complained of diarrhoea, four of nausea, six of vomiting and six of heartburn; in the placebo group two complained of diarrhoea, one of nausea, 10 of vomiting, six of heartburn and one of fullness.

Five women in the magnesium group and three women in the control group had a miscarriage.

Median maternal weight increase was 11 kg in both groups and there were no statistically significant differences in maximum systolic and diastolic blood pressures or in oedema between the two groups (Table 2).

In the magnesium group 44 women were hospitalized for 533 days. In the placebo group 65 women spent 887 days in hospital. Of the indications for admission to hospital, haemorrhage during pregnancy, incompetent cervix and preterm labour were more frequent in the placebo group, the difference was statistically significant. The average duration of each admission to hospital was similar in the two groups and so were the number of miscarriages (Table 3).

The median gestation was significantly longer in the women treated with magnesium, although the difference between the medians was not more than 1 day. This difference was particularly notable when the preterm deliveries (< 37 weeks) are compared (Table 4). There were no differences between the groups in the duration of the first stage of labour. Although the second stage of labour was longer and operative delivery more frequent in the magnesium-treated group than in the placebo group, these differences were not statistically significant (Table 4).

Differences between the two groups in respect of placental weight, infant weight and length, frequency of low Apgar scores (≤7) and low birthweight are shown in Table 5. These differences reflect the decreased frequency of preterm delivery associated with magnesium supplementation but they do not reach statistical significance. There were no differences between the groups in infant head circumference or in neonatal acid base values. Significantly fewer infants in the group receiving magnesium were admitted to the neonatal intensive care unit. The biggest differences were found in the admission rates for preterm birth and asphyxia (Table 5).

There was one perinatal death in the magnesium group. The mother was a 40-year-old diabetic in her first pregnancy. She was hospitalized twice, in early pregnancy because of haemorrhage and hyperemesis gravidarum and again in later pregnancy because of the diabetes and preterm labour. A growth-retarded fetus was born at 33 weeks gestation by forceps after severe fetal bradycardia and died immediately after delivery because it proved impossible to oxygenate the infant sufficiently.

In the subsidiary analysis we excluded all those women who did not fulfil the protocol of medication as prescribed. After these exclusions, 217 women remained in the magnesium

Table 1. Characteristics of the two groups of women recruited to the study

	Magnesium group (*n*=278) Centile			Placebo group (*n*=290) Centile		
Variable	5th	50th	95th	5th	50th	95th
Age (years)	20·3	28·2	37·9	19·5	28·0	34·6
Parity	1	2	3	1	2	3
Gravidity*	1	2	5	1	2	5
Birthweight of 1st child (g)	2500	3250	3915	2200	3280	4020
Duration of 1st pregnancy (weeks)	37	40	42	36	40	42

* The present pregnancy is included There were no significant differences between the two groups

Table 2. Clinical details of women treated with magnesium or placebo during pregnancy

	Magnesium group Centile			Placebo group Centile			
Variable	5th	50th	95th	5th	50th	95th	Significance
Number of tablets/day	3	6	6	3	6	6	NS
Duration of medication (days)	53	182	217	32	168	224	<0·01
Total number of tablets	266	1050	1302	189	966	1344	<0·01
Weight gain (kg)	5	11	18	4	11	19	NS
Maximum blood pressure (mmHg)							
Systolic	107	125	135	108	124	136	NS
Diastolic	61	73	85	61	73	87	NS
No. with oedema (subjective)							
+		59			79		NS
++		15			15		NS
+++		3			1		NS
Total (*n*)		77			95		NS

NS, Not significant.

Table 3. Indications for hospitalization during pregnancy in women treated with magnesium or placebo

Variable	Magnesium group	Placebo group	Significance
Number of admissions to hospital (*n*)	48	80	—
Number of women hospitalized (*n*)	44	65	<0·05
Time spent in hospital (days)			
Total length	533	887	—
Median length/patient	7·5	7·0	NS
Indications coded (*n*)			
Haemorrhage	4	17	<0·01
Threatened miscarriage	3	2	NS
Incompetent cervix	8	17	<0·05
Preterm labour	12	26	<0·05
Premature membrane rupture	1	1	NS
Urinary tract infection	4	2	NS
Diabetes	1	0	NS
Pre-eclampsia	2	2	NS
Twin pregnancy	1	2	NS
Fetal growth retardation	0	3	NS
Not encoded	12	8	—
Miscarriage	5	3	NS

NS, Not significant.

Table 4. Mode of delivery in the study groups

	Magnesium group Centile			Placebo group Centile			
Variable	5th	50th	95th	5th	50th	95th	Significance
Gestational age at delivery (weeks/days)	37/3	40/0	41/6	35/1	39/6	41/6	<0·05
Delivery before 37 weeks (*n*)		7			14		NS
Length of 1st stage (h)	2	6	13	2	6	15	NS
Length of 2nd stage (min)	5	19	100	5	18	90	NS
Operative delivery (*n*)		70			55		NS

NS, Not significant.

Table 5. Fetal outcome in women treated with magnesium or placebo during pregnancy

	Magnesium group Centile			Placebo group Centile		
Variable	5th	50th	95th	5th	50th	95th
Placental weight (g)	400	580	800	390	570	800
Birthweight (g)	2530	3325	4270	2280	3300	4120
No. < 2500g		12			19	
No < 1500g		3			6	
No. < 10th centile		30			33	
Infant length (cm)	46	50	53	45	49	53
Head circumference (cm)	32	34	37	32	34	37
Umbilical blood pH						
Artery	7·17	7·28	7·37	7·17	7·28	7·36
Vein	7·23	7·33	7·44	7·24	7·35	7·44
No. with Apgar score ≤7						
at 1 min		42			47	
at 5 min		3			8	
at 10 min		1			5	
Admitted to intensive care (*n*)		20			36*	
Indications coded (*n*)						
Preterm birth		4			8	
Growth retardation		5			6	
Prolonged asphyxia		2			5	
Observation		3			3	
Respiratory insufficiency		2			2	
Rh-incompatibility		0			2	
Jaundice		2			4	
Malformation						
face		0			1	
abdomen		0			1	
multiple		1			1	
Metabolic disease		0			1	
Fits after delivery		1			0	
Not encoded		0			2	
Perinatal death		1			0	

* Significantly different between the two groups $P<0{\cdot}01$.

Table 6. Comparison between magnesium and placebo groups after exclusion of patients who did not take their tablets regularly*

	Magnesium group (n=217) Centile			Placebo group (n=220) Centile			
Variable*	5th	50th	95th	5th	50th	95th	Significance
Birthweight (g)	2610	3340	4285	2245	3300	4110	<0·05
No. <2500g		6			18		<0·05
No. <1500g		0			6		<0·05
Infant length (cm)	46	50	53	44·5	49	53	<0·05
Head circumference (cm)	33	35	37	31	34	36·5	<0·05
No. with 10-min Apgar score ≤7		0			5		<0·05
No. of women hospitalized		26			48		<0·01
No. with oedema grade+		42			63		<0·05

* Only the variables with better significance than in the main analysis are listed.

group and 220 in the placebo group. Some of the differences that only reflected a trend in the main study became statistically significant and some of the differences that were already significant in the main study were confirmed at a higher level of significance (Table 6).

Discussion

We found no evidence of a protective effect of magnesium supplementation on the frequency of pre-eclampsia and to be able to address this question the study groups would have had to have been considerably bigger. Similarly, the observation that a very early start of magensium supplementation is associated with a decreased rate of early miscarriage (Kiss *et al.* 1981) could not be assessed because insufficient numbers of women joined the study early enough and there were no statistically significant differences in the frequency of miscarriage between the groups

In spite of a relatively small difference of only 1 day between the median lengths of gestation, this difference is significant at the 5% level. This is due to fewer preterm deliveries in the magnesium group, an observation which confirms our second hypothesis. Although this difference was reflected in a reduction in the frequency of low birthweight, there was no evidence that magnesium supplementation had any effect on fetal growth as such.

Nevertheless magnesium supplementation was associated with a significant reduction in maternal and fetal morbidity both before and after delivery. It seems reasonable to suppose that the specific magnesium depletion in pregnant women may be compensated by magnesium replacement. More than 300 enzymatic reactions depend on magnesium (Günther 1981). The results of this study suggest that magnesium supplementation during pregnancy may have important benefits.

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References

Conradt, A., Weidinger, H. & Algayer, H. (1984) On the role of magnesium in fetal hypotrophy, pregnancy induced hypertension and pre-eclampsia. *Mag Bull* **6**, 68-76

Dumont, M. M. (1965) Traitement des douleur uterines gravidique par le lactate de magnesium. *Lyon Med* **213**, 1571-1582.

Gunther, T. (1981) Biochemistry and pathobiochemistry of magnesium. *Mag Bull* **3**, 91-101.

Kiss, V., Balasz, M , Morvay, F , Varenka, Z , Szekely, A. & Szucs, M. (1981) Effect of maternal magnesium supply on spontaneous abortion and premature birth and on intrauterine foetal development experimental epidemiological study. *Mag Bull* **3**, 73-79.

Largo, R H., Walli, R., Duc, G., Fanconi, A & Prader, A. (1980) Evaluation of perinatal growth. *Helv Paediatr Acta* **35**, 419-436

Selbmann, H. K., Brach, M., Elser, H., Holzmann, K., Johannigmann, J & Riegel, K. (1980) *Munchner Perinatal-Studie 1975–1977* Deutscher Arzte-Verlag, Köln, p. 242.

Spatling, L. (1981) Orale Magnesiumzusatztherapie bei vorzeitiger Wehentatigkeit *Geburtshilfe Frauenheilkd* **41**, 101-102.

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The effect of the antiprogestin RU 486 on uterine contractility and sensitivity to prostaglandin and oxytocin

M. L. SWAHN, M. BYGDEMAN

Summary. The effect of RU 486, a steroid acting as an antiprogestin at the receptor level, on uterine contractility and sensitivity to the prostaglandin analogue, 16-phenoxy-PGE$_2$ methyl sulfonylamide (16-phenoxy-PGE$_2$) and to oxytocin was studied in 29 women in early pregnancy. Seven untreated women at the same stage of pregnancy served as controls. In the untreated women no spontaneous uterine contractility was recorded and the response to 0·25 mg 16-phenoxy-PGE$_2$ was characterized by an increase in uterine tonus with superimposed irregular contractions of low amplitude. Treatment with 25 mg RU 486 twice daily resulted in the appearance of regular uterine contractions at 24 h in two out of five patients and in all patients at 36, 48 and 72 h after the start of RU 486 treatment. The withdrawal of progesterone influence changed the inactive early pregnant uterus into an active organ. Administration of 16-phenoxy-PGE$_2$ caused an obvious stimulation of both frequency and amplitude of the contractions. In addition, the significantly increased sensitivity to the prostaglandin analogue, but not to oxytocin, was already apparent 24 h after the start of RU 486 treatment. We have previously shown that the addition of one intramuscular injection of 16-phenoxy-PGE$_2$ on the fourth day of treatment with RU 486 (25 mg twice daily) significantly increased the abortifacient effect of the antiprogestin during early pregnancy. The present study suggests that a shorter treatment may be possible.

The contractility of the non-pregnant and pregnant human uterus is regulated by hormones and changes in the contractility pattern during the menstrual cycle are related to the plasma levels of the ovarian steroids, oestrogen and progesterone (Hein *et al.* 1973; Moawad & Bengtsson 1967). During early human pregnancy, uterine activity is decreased and the response to oxytocin is suppressed due to a blocking effect of luteal progesterone (Csapo 1970; Csapo *et al.* 1973*a*). Csapo *et al.* (1972, 1973*a,b*) showed that lute-ectomy before the luteo-placental shift and the subsequent decrease in plasma progesterone resulted in increased contractility of the uterus and subsequent spontaneous abortion. Csapo (1974) proposed that the degree of uterine activity during pregnancy is regulated by the balance between the intrinsic suppressor, progesterone, and the stimulant, prostaglandin F$_{2\alpha}$ (PGF$_{2\alpha}$).

RU 486 (Roussel-Uclaf, Paris) is a steroid with a high, reversible binding affinity to the progesterone and glucocorticoid receptor. The substance thus acts as a local antiprogestin in the

Department of Obstetrics and Gynecology, Karolinska Hospital, S-104 01 Stockholm, Sweden
M L SWAHN
M. BYGDEMAN

Correspondence: M. L. Swahn

decidua, endometrium, and myometrium (Baulieu 1985). We have previously presented preliminary evidence that local withdrawal of progesterone by administration of RU 486 to women in early pregnancy resulted in an increased, spontaneous uterine activity and enhanced sensitivity to the prostaglandin analogue, 16-phenoxy-PGE$_2$ (Schering AG, West Berlin). Sequential therapy with RU 486 and this prostaglandin analogue was also more effective in terminating early pregnancy than treatment with RU 486 alone (Bygdeman & Swahn 1985; Swahn *et al.* 1985).

The aim of this study was to assess the duration of RU 486 treatment needed to induce an increase in uterine contractility and sensitivity to prostaglandin and oxytocin.

Subjects and methods

The study was approved by the Swedish Drug Regulatory Authorities and the ethics committee of the Karolinska hospital.

A total of 36 women in early pregnancy, admitted to the hospital for termination, was recruited to the study after their informed consent had been obtained. All women had a normal pregnancy as judged from gynaecological examination and plasma β-hCG assay; none had used an intrauterine contraceptive device or steroidal contraceptive during the cycle of conception.

The women were divided into a control and a treatment group. The control group consisted of seven untreated women in whom uterine contractility was recorded for 3–4 h. After an initial period of at least 30 min to record the spontaneous activity of the uterus, graded intramuscular doses (from 0·05 to 0·25 mg) of 16-phenoxy-tetranor-PGE$_2$ methyl sulfonylamide (16-phenoxy-PGE$_2$) were given to five patients. The remaining two patients received intravenous bolus injections of oxytocin in increasing doses of 1, 2, 4 and 8 i.u. The usual interval between the injections of 16-phenoxy-PGE$_2$ and oxytocin was 30 min. After the end of the recording session the pregnancy was terminated by vacuum aspiration.

The treatment group consisted of 29 women who received 25 mg RU 486 twice daily for 4 days. Intrauterine pressure recording in these women was scheduled to start 24, 36, 48 or 72 h after the intake of the first RU 486 tablet, but recordings were cancelled if there were clinical signs of imminent abortion. Thus, four women scheduled for recording at 72 h could not be studied since they started to bleed during the night preceding the recording. In addition, two subjects in this treatment group were excluded retrospectively as they aborted during the recording. Another two women were excluded retrospectively, one in the 36-h and one in the 48-h group, as the transducer was expelled. Since the exclusion rate was much higher at 72 h than at 24, 36 and 48 h, the remaining patients in the 72-h group are not strictly comparable to the patients in the other treatment groups. The results of the recordings from the patients after 72 h pretreatment with RU 486 were therefore not included in the anaylsis of the data. Of the remaining 21 women, 19 received 16-phenoxy-PGE$_2$ in the same way as the women in the control group but the two highest doses (0·20 and 0·25 mg) were omitted if the lower doses (0·05, 0·10 and 0·15 mg) resulted in strong uterine contractions. Two women recorded at 72 h after the start of RU 486 treatment received intravenous bolus injections of oxytocin with the same regimen as used in the control group.

Uterine contractility was recorded using a Grass Polygraph connected to a pressure transducer (Millar Microtip PC-771) which was inserted extra-amniotically through the cervical canal into the upper part of the uterus with its tip 1–2 cm from the fundus. The transducer was secured in position by a vaginal tampon and the women were kept supine during the recording. The degree of uterine contractility was quantified by planimetric measurement of the total pressure area (TPA) per 10-min period (mmHg/10 min) and by calculating Montevideo units (MU). The values given in Fig. 2 and the text under Results refer to the mean uterine activity during the previous 10-min period. The differences in spontaneous uterine contractility and the effect of the PGE$_2$ analogue between control and treatment groups were evaluated statistically by using the two-tailed Wilcoxon two-sample rank test (the Mann–Whitney test). Differences with a value of $P<0{\cdot}05$ were regarded as significant.

Results

Mean age, duration of pregnancy at the time of recording, number of pregnancies, and parity did not differ between the women in the control group and those in the treatment group receiving 16-phenoxy-PGE_2 (Table 1).

In control women, little or no spontaneous uterine activity was observed. Mean TPA was 5·8 (SEM 1·3) mmHg/10 min and the baseline uterine activity (UA) was 5·5 (SEM 3·9) MU. After administration of 16-phenoxy-PGE_2 there was an increase in uterine tonus on which irregular contractions of low amplitude were superimposed. The response was dose related. Mean TPA was 24 (SEM 7·4) mmHg/10 min and mean UA 49 (SEM 23·8) MU at 30 min after administration of 0·05 mg of the E-analogue. The corresponding values at 30 min after 0·25 mg were 50 (SEM 14·5) mmHg/10 min and 258 (SEM 109) MU, respectively (Figs 1 & 2, Table 2). None of these women experienced pain associated with the increase of uterine activity.

In the group treated with RU 486, 24 h after the start of treatment, the uterus was still inactive in three women while in the other two spontaneous uterine contractility was present (Fig. 3). The mean uterine activity immediately before the first injection of 16-phenoxy-PGE_2 was 50 (SEM 33·6) MU and the TPA 6 (SEM 1·4) mmHg/10 min (Table 2). In all women the response to 16-phenoxy-PGE_2 was qualitatively and quantitatively different from that found in the control group. With the lowest 0·05 mg dose of the analogue an increase in uterine tonus was observed with more co-ordinated contractions superimposed. TPA and UA at 30 min after the lowest dose of prostaglandin were 46 (SEM 8·4) mmHg/10 min and 300 (SEM 152) MU, respectively. The contractility increased further with higher doses. With 0·15 mg 16-phenoxy-PGE_2 the corresponding values were 65 (SEM 7·1) mmHg/10 min and 529 (SEM 127) MU. The increase in uterine response in comparison to the control group was statistically significant 30 min after the 0·05 mg dose of 16-phenoxy-PGE_2 when measured in MU, while for TPA a significant difference was reached 20 min after the 0·1 mg dose (Fig. 2).

After 36 and 48 h of treatment with RU 486 all patients had developed spontaneous uterine contractions which were significantly different from the control group. TPA was 16·2 (SEM 5·2) and 11·8 (SEM 4·0) mmHg/10 min and UA 222 (SEM 93) and 175 (SEM 60) MU at 36 and 48 h after the start of treatment with RU 486, respectively (Fig. 2, Table 2). For 72 h the corresponding values were 10 mmHg/10 min and 172 MU. Uterine sensitivity to the PGE_2 analogue had also changed.

After intramuscular injections of 16-phenoxy-PGE_2 an increase in uterine tonus and obvious stimulation of the frequency and amplitude of the contractions were observed (Fig. 4). The uterine response to 16-phenoxy-PGE_2 was significantly more pronounced after treatment with RU 486 than in the untreated women (Fig. 2, Table 2). In some treated women moderate to strong lower abdominal pain was induced by as little as 0·15 mg 16-phenoxy-PGE_2 In these subjects the higher doses of the analogue were omitted. It is our impression that the pain reaction was more common in women recorded at 48 h than in those recorded at 72 h There was, however, no difference in degree of spontaneous contractility or in uterine sensitivity to 16-phenoxy-PGE_2 between the subjects recorded at 36 and 48 h. The data obtained after 72 h pretreatment with RU 486 were similar to those at 36 and 48 h.

Intravenous injections of oxytocin in the two

Table 1. Characteristics of the women in the control group and RU 486-treated group who received 16-phenoxy-PGE_2

	No. of patients	Mean age (years)	Mean duration of pregnancy (days)	Mean no of previous pregnancies	Mean parity
Control group	5	31 2	48·6	2·6	0 8
Treatment group					
Hours between start of RU 486 treatment and recording:					
24	5	31·6	44 6	2·8	1·2
36	5	34·4	47·6	2·5	0·8
48	5	34·2	48·2	3·0	1·0
72	4	34·2	50·2	3·2	1·2

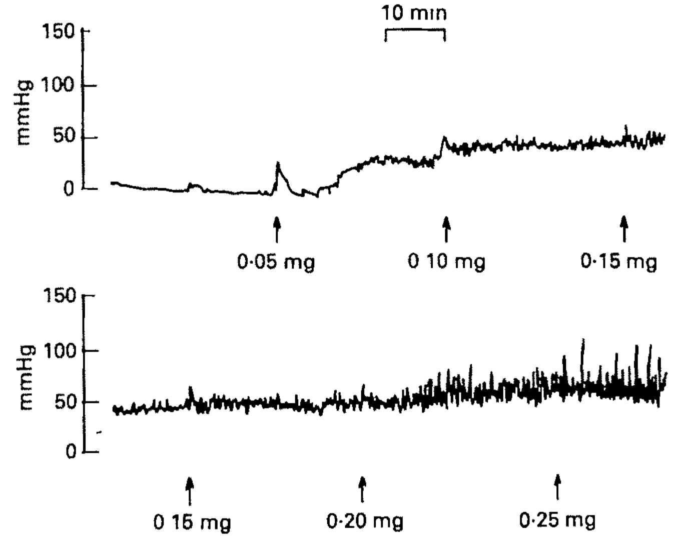

Fig. 1. Spontaneous uterine contractility and response to repeated intramuscular injections of 16-phenoxy-PGE$_2$ in untreated women in early pregnancy The interval between the two 0·15 mg doses was duplicated at the cutting of the tracing

women in early pregnancy not treated with RU 486 resulted in a rapid but short-lasting increase in uterine tonus. With 4 and 8 i.u. oxytocin a slight increase in amplitude and frequency of contractions could be observed (Fig. 5). In the two women recorded at 72 h after the start of treatment with RU 486, spontaneous uterine contractions were observed but the uterine response to intravenous injections of oxytocin was the same as that seen in the untreated women. Control injections of 16-phenoxy-PGE$_2$ given towards the end of the recording session confirmed the increased uterine sensitivity to prostaglandin.

Discussion

The present study included 36 normal women admitted to hospital for termination of early normal pregnancy. The aim of the study was to assess the effect of RU 486 on spontaneous uterine contractility and on sensitivity of the myometrium to 16-phenoxy-PGE$_2$ and to oxytocin. In spite of precautions taken to avoid displacement of the transducer, it was expelled in two women.

To measure uterine contractility reliably, abortion must not be imminent at the time of the recording. This requirement caused problems for the recordings scheduled at 72 h after the start of RU 486 treatment as four women had vaginal bleeding that was considered to be too heavy and the recording was cancelled. These subjects were excluded along with two additional women who, in fact, aborted during the recording session in spite of these precautions. The remaining women may, therefore, represent a population of subjects who are less sensitive to RU 486 therapy and were thus excluded from the comparative statistical calculations. However, duration of pregnancy was the same as for the women in the other treatment groups.

The degree of uterine activity was quantified in two ways, in Montevideo units (MU) and in total pressure area (TPA). The former method reflects the increase in frequency and amplitude of the contractions whereas the latter method also includes the effect on uterine tonus.

There were several reasons for choosing 16-phenoxy-PGE$_2$ to test the sensitivity of the myometrium. Given intramuscularly this analogue is rapidly absorbed (Hümpel *et al.* 1978) which permits repeated injections to be given. Since the recordings were performed between 24 and 72 h after the start of RU 486 treatment it was expected from previous studies (Swahn *et al* 1985) that vaginal bleeding would start during the recording session in some subjects. By choosing the intramuscular instead of the vaginal route of administration, disturbances in absorption due to vaginal bleeding could be

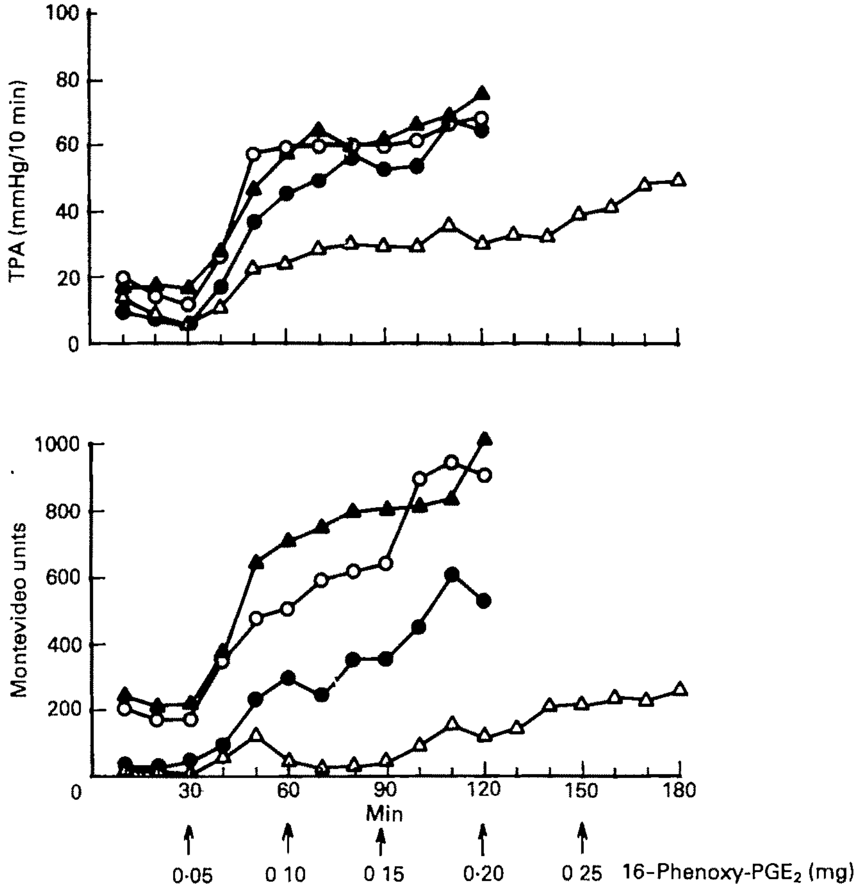

Fig. 2. Effect of increasing intramuscular doses of 16-phenoxy-PGE$_2$ on uterine contractility measured as total pressure area (TPA) and in Montevideo units (MU) in early pregnancy in untreated women (△), and 24 (●), 36 (▲), and 48 (○) h after the start of treatment with RU 486, 25 mg twice daily The difference between untreated and treated women was significant ($P<0{\cdot}05$).

avoided and permit a more accurate comparison between the different treatment groups.

No spontaneous contractions were recorded in the control group. During treatment with RU 486 uterine contractility developed gradually as described previously (Swahn *et al.* 1985; Bygdeman & Swahn 1985). Already 24 h after the start of treatment spontaneous contractions were present in two of five women. After 36, 48 and 72 h of RU 486 treatment all women showed spontaneous uterine activity. The interval of 24–36 h between the start of treatment and the appearance of contractions was similar to that reported following lute-ectomy during early pregnancy (Csapo *et al.* 1973*a*) indicating that RU 486 is as effective in causing a local withdrawal of progesterone influence as removal of the main source of progesterone secretion. Since it has been shown previously that treatment with the same dose of RU 486 affected plasma progesterone levels only marginally during the first 4 days of therapy (Kovacs *et al.* 1984), the present observation of increased uterine activity after 24–36 h of antiprogestin therapy suggests that the effect of progesterone on uterine contractility is likely to be mediated through the receptor system. That progesterone is of importance for the regulation of uterine contractility

Table 2. Uterine contractility measured as total pressure area (TPA) and in Montevideo units (MU) in untreated women (control group) and in women treated with 25 mg RU 486 twice daily The recordings were obtained 24, 36 and 48 h after the start of RU 486 treatment

	Control period	16-phenoxy-PGE_2 (mg)				
		0·05	0·1	0·15	0·2	0·25
Control group ($n = 5$)						
TPA	5·8 (1·3)	24·0 (7·4)	29·2 (8·0)	30·2 (8·9)	39·5 (8·7)	49·6 (14·5)
MU	5·5 (3·9)	49·0 (23·8)	45·2 (22·3)	122 (28)	219 (62)	258 (109)
RU 486 24 h ($n = 5$)						
TPA	6·0 (1·4)	45·6 (8·4)*	52·8 (6·2)*	64·8 (7·1)*		
MU	50·0 (33·6)	300 (152)*	356 (66)*	529 (127)*		
RU 486 36 h ($n = 5$)						
TPA	16·2 (5 2)*	57·6 (5·7)*	61·2 (2·5)*	76·3 (10·6)*		
MU	222 (93)*	711 (136)*	806 (110)*	1023 (233)*		
RU 486 48 h ($n = 5$)						
TPA	11·8 (4·0)*	59·0 (6·4)*	60·6 (5·0)*	66·8 (4·4)*		
MU	175 (60)*	502 (76)*	636 (107)*	910 (116)*		

Results are means (SEM) values of uterine contractility/10 min for the 20–30 min interval after each prostaglandin injection given intramuscularly every 30 min in increasing doses from 0·05–0·25 mg.

* Significantly different from corresponding values in control group

has recently also been shown by Webster *et al.* (1985*a*) using epostane, a competitive inhibitor of the 3β-hydroxy steroid dehydrogenase enzyme system (Pattison *et al.* 1985). Both our study and that of Webster *et al.* (1985*a*) are in accordance with the concept proposed by Csapo *et al.* (1973*a*) that the early pregnant uterus is a suppressed organ and that progesterone withdrawal releases the suppression and converts the uterus into a spontaneously active organ.

The mechanism of progesterone inhibition of uterine contractility is not fully understood. Progesterone might influence calcium binding to the cellular membrane resulting in decreased excitability and reduced propagation of the contractile stimulus. The inhibitory effect of progesterone on the formation of oestradiol receptors (Hsueh *et al.* 1975), and of intercellular gap junctions in the myometrium (Garfield *et al.* 1979; Garfield & Hayashi 1981) demonstrated in animal studies, and the hormone's stimulatory effect on the formation of β-adrenoreceptors (Roberts *et al.* 1981) in the myometrium may also be of importance. The

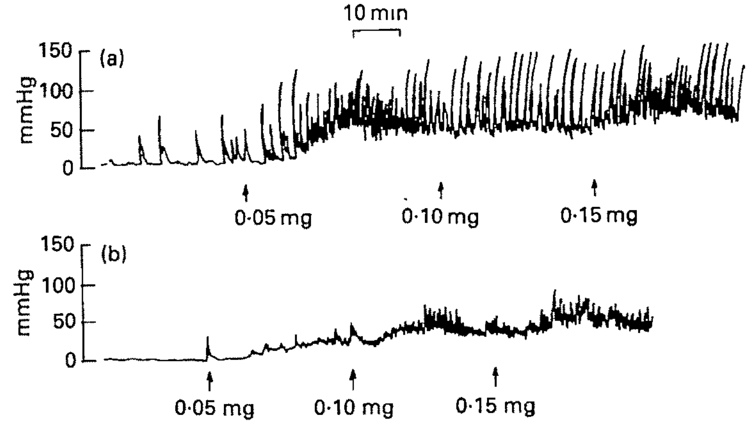

Fig. 3. Uterine contractility in two women in early pregnancy 24 h after the start of treatment with 25 mg RU 486 twice daily In one woman (a) spontaneous uterine contractions have started to appear, while in the other woman (b) the uterus is still inactive. The arrows indicate intramuscular injection of increasing doses of 16-phenoxy-PGE_2

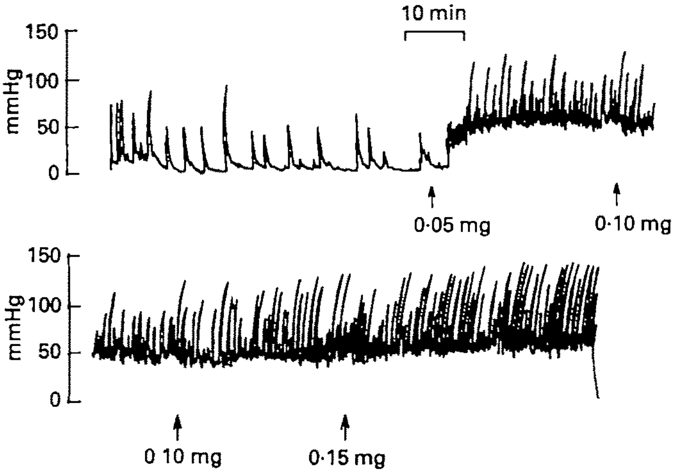

Fig. 4. Uterine contractility in a woman in early pregnancy 48 h after start of treatment with 25 mg RU 486 twice daily The arrows indicate intramuscular injection of increasing doses of 16-phenoxy-PGE$_2$. The interval between the two 0·1 mg doses was duplicated at the cutting of the tracing

development of gap junctions is believed to enhance electrical conductivity and, thus, co-ordinated uterine activity. There are also reasons to believe that progesterone enhances the stability of the lysosomal membranes (Gustavii 1975). A local decrease in progesterone concentration may thus facilitate the release of lysosomal phospholipase A and initiate an increased, endogenous PG production resulting in stimulation of uterine contractility (Gustavii 1975). However, the clinical finding (Bygdeman & Swahn 1985) that adjuvant PG therapy is required to obtain a high frequency of complete abortion indicates that, if endogenous prostaglandins are important for the appearance of co-ordinated uterine contractions, they are not

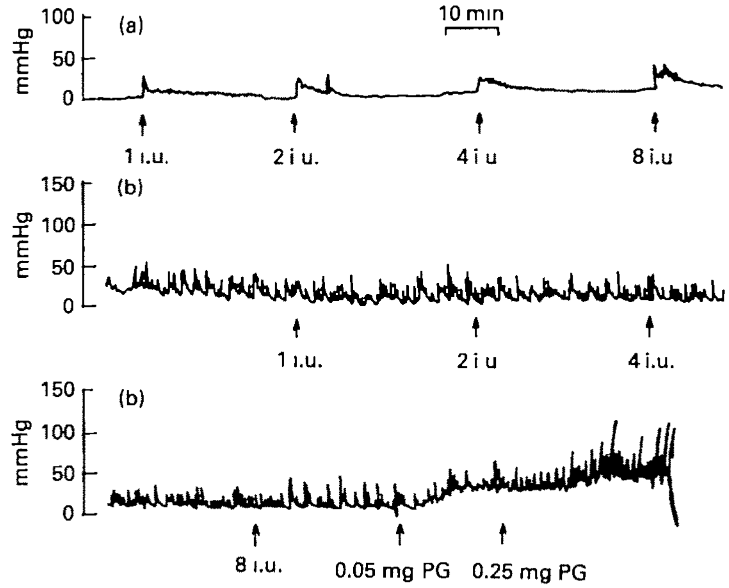

Fig. 5. Uterine contractility and effect of intravenous injections of oxytocin in one control subject (a) and in one subject treated with 25 mg RU 486 twice daily for 72 h (b). The RU 486 treated woman was also given two doses of 16-phenoxy-PGE$_2$ (↑ PG).

always sufficiently effective to cause expulsion of the conceptus.

Administration of 16-phenoxy-PGE_2 to the women not treated with RU 486 caused an increase in uterine tonus upon which irregular contractions of low amplitude were superimposed. As early as 24 h after the start of RU 486 therapy the response to the PG analogue was quite different. The sensitivity of the myometrium was markedly increased and 16-phenoxy-PGE_2 now caused an obvious stimulation of both amplitude and frequency of the contractions. It is noteworthy that the same response was also found in the three women in whom spontaneous uterine activity had not yet increased. These results indicate that an increased sensitivity to prostaglandin precedes the activation of the myometrium. Prolonging the duration of RU 486 treatment to 36 and 48 h tended to further increase the sensitivity to 16-phenoxy-PGE_2, but the difference was not statistically significant. Thus, treatment with RU 486 for 72 h did not show any advantage over the 36- and 48-h treatment with regard to either induction of spontaneous uterine contractions or sensitivity to prostaglandin, although the high drop-out rate of subjects at 72 h might have influenced the results. An increase in sensitivity has also been demonstrated for $PGF_{2\alpha}$ after luteectomy (Csapo *et al.* 1973*a*) and for PGE_2 after treatment with epostane (Webster *et al.* 1985*b*).

Like Webster *et al.* (1985*a*), who used epostane, we found no increased sensitivity to oxytocin after treatment with RU 486. One reason could be that functional levels of receptors for PGE_2 but not for oxytocin are present during early pregnancy (Fuchs *et al.* 1984). Theoretically, the antiglucocorticoid effect of RU 486 could also be important. Elger *et al.* (1987) have shown that the abortifacient effect of RU 486 in the guinea-pig is enhanced by the addition of 16-phenoxy-PGE_2. Such synergism, however, was not found when another antiprogestin, ZK 98·734 (Schering AG, West Berlin), which has a lower antiglucocorticoid effect than RU 486, was used.

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References

Baulieu, E E (1985) RU 486—an antiprogestin steroid with contragestive activity in women In *The Antiprogestin Steroid RU 486 and Human Fertility Control* (Baulieu, E. E. & Segal, S. J , eds), Plenum Press, New York, pp. 1-25

Bygdeman, M. & Swahn, M L. (1985) Progesterone receptor blockage. Effect on uterine contractility in early pregnancy. *Contraception* **32,** 45-51.

Csapo, A. J. (1970) The diagnostic significance of the intrauterine pressure *Obstet Gynecol Surv* **25,** 515-543.

Csapo, A. J , Pulkkinen, M. O , Ruttner, B., Sauvage, J P & Wiest, W G. (1972) The significance of the human corpus luteum in pregnancy maintenance *Am J Obstet Gynecol* **112,** 1061-1067.

Csapo, A J., Pulkkinen, M O & Kaihola, H L (1973*a*) The effect of luteectomy induced progesterone withdrawal on the oxytocin and prostaglandin response of the first trimester pregnant uterus *Prostaglandins* **4,** 421-429

Csapo, A. J., Pulkkinen, M. O & Wiest, W G. (1973*b*) Effects of luteectomy and progesterone replacement therapy in early pregnant patients *Am J Obstet Gynecol* **115,** 759-765

Csapo, A. J. (1974) 'Prostaglandin impact' for menstrual induction *Popul Rep [G]* **4,** G33-G40.

Elger, W , Qing, S. S., Fahnrich, M., Beier, S , Chwalisz, K , Henderson, D., Neef, G. & Rohde, R. (1987) The mechanism of action of new antiprogestins. In *Fertility Regulation Today and Tomorrow* (Diczfalusy, E. & Bygdeman, M , eds), Raven Press, New York (in press).

Fuchs, A.-R., Fuchs, F., Husslein, P & Soloff, M. S. (1984) Oxytocin receptors in the human uterus during pregnancy and parturition *Am J Obstet Gynecol* **150,** 734-741

Garfield, R. E., Rabideau, S , Challis, J R. G. & Daniel, E. E. (1979) Hormonal control of gap junction formation in sheep myometrium during parturition *Biol Reprod* **21,** 999-1007.

Garfield, R E. & Hayashi, R H. (1981) Appearance of gap junctions in the myometrium of women during labor. *Am J Obstet Gynecol* **140,** 254-260

Gustavii, B. (1975) Release of lysosomal acid phosphatase into the cytoplasm of decidual cells before the onset of labour in humans *Br J Obstet Gynaecol* **82,** 177-181.

Hein, P. R., Eskes, T. K. A., Stolte, L A M , Braaksma, J T., Janssens, J. & van den Hoek, J. M. (1973) The influence of steroids on uterine motility in the non pregnant uterus. In *Uterine Contractility—Side Effects of Steroidal Contraceptives* (Josimovich, J. B , ed.) John Wiley & Sons, New York, pp. 107-140

Hsueh, A. J. W., Peck, J. E. J. Jr & Clark, J H. (1975) Progesterone antagonism of the oestrogen receptor and oestrogen-induced uterine growth. *Nature* **254,** 337-339.

Hümpel, M., Pommerenke, G & Weiss, C. (1978) Pharmacokinetics and metabolism of sulprostone in women. In *International Sulprostone Symposium, Vienna 1978* (Friedel, K., Schneider, A & Wurfel, H., eds), Medico-Scientific Series of Schering AG, Berlin, Bergkamer, pp. 55-59.

Kovacs, L., Sas, M., Resch, B. A., Ugocsai, G., Swahn, M L., Bygdeman, M. & Rowe, P. J. (1984) Termination of very early pregnancy by RU 486, an antiprogestational compound. *Contraception* **29,** 399-410.

Moawad, A. H & Bengtsson, L. P (1957) In-vivo studies of the motility patterns of the nonpregnant human uterus. The normal menstrual cycle. *Am J Obstet Gynecol* **98,** 1057-1064

Pattison, N. S., Webster, M A., Phipps, S. L., Andersson, A. B. M & Gillmer, M. D G. (1985) Inhibition of 3β-hydroxy steroid dehydrogenase activity in first and second trimester human pregnancy and the luteal phase using Epostane. *Fertil Steril* **42,** 875-881.

Roberts, J. M., Insel, P. A. & Goldfien, A. (1981) Regulation of myometrial adrenoreceptors and adrenergic response by sex steroids. *Mol Pharmacol* **20,** 52-58.

Swahn, M. L , Cekan, S., Wang, B., Lundstrom, V. & Bygdeman, M. (1985) Pharmacokinetic and clinical studies of RU 486 for fertility regulation. In *The Antiprogestin Steroid RU 486 and Human Fertility Control* (Baulieu, E. E & Segal, S. J., eds), Plenum Press, New York, pp. 249-258.

Webster, M. A., Pattison, N. S , Phipps, S L. & Gillmer, M. D. G. (1985*a*) Myometrial activity in first trimester human pregnancy after epostane therapy. Effect of intravenous oxytocin *Br J Obstet Gynaecol* **92,** 957-962.

Webster, M. A., Phipps, S L. & Gillmer, M D. G. (1985*b*) Interruption of first trimester human pregnancy following epostane therapy Effect of prostaglandin E_2 pessaries. *Br J Obstet Gynaecol* **92,** 963-968

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Does mother know best? Maternal assessment of relative fetal size *in utero*

DAVID R. WHITE

Summary. The accuracy of pregnant womens' impressions of the size of their babies *in utero* relative to their previous babies has been assessed in 140 parous women. The women who thought their babies would be bigger gave birth to babies weighing a mean of 0·30 kg more than their previous babies ($P<0\cdot01$) and the women who thought their babies would be smaller were delivered of babies weighing a mean of 0·22 kg less than their previous babies ($P<0\cdot01$).

Many pregnant women claim that they are able to detect differences in the size of babies *in utero* between one pregnancy and the next. Some obstetricians when assessing fetal size antenatally ask the pregnant woman whether the fetus that she is carrying seems larger or smaller than her previous baby at the same stage of pregnancy, and the present study set out to determine the accuracy of that recollection.

If the mother's impression of relative fetal size between one pregnancy and another is accurate, it could be of use in screening pregnancies for small-for-gestational-age (SGA) fetuses or in avoiding problems of feto–maternal disproportion in women with abnormal presentations or uterine scars.

Subjects and methods

All parous women attending the antenatal clinic at Raigmore Hospital during a 4-month period were included in the study. Women whose previous pregnancies had ended before 36 completed weeks gestation or with a stillbirth and those whose previous or present pregnancy was multiple were excluded, leaving a total of 140 women in the analysis. Each woman after reaching 34 weeks gestation was asked to compare the size of her fetus with the size of her previous baby at the same stage of pregnancy and to indicate whether she thought it was larger, smaller or about the same size.

Birthweights and gestational ages at delivery were recorded in the study pregnancies and for the previous pregnancies. Each birthweight was converted to a standard deviation score for its gestation and this score was then converted back to a full term birthweight using the nomograms of Altman & Coles (1980). Thus babies born at different gestational ages could be directly compared. The women were divided into three groups according to their estimates of the babies' relative sizes. The differences in birthweight between the present and previous pregnancies in the three groups of women were compared using the paired *t*-test and the differences in the distribution of birthweight differences were compared between the three groups using the *t*-test.

The value of the mother's impression as a means of detecting differences in fetal size was assessed by calculating the sensitivity, specificity and predictive values of each response (Stempel 1982).

Results

The women who thought their babies would be larger had babies with an average birthweight

Department of Obstetrics and Gynaecology, Raigmore Hospital, Inverness
DAVID R. WHITE *Registrar*

Correspondence: Mr D. R. White, Senior Registrar, Liverpool Maternity Hospital, Oxford Street, Liverpool

Table 1. Distributions and means of differences in birthweights between study and previous pregnancies in relation to mothers' impressions of size of fetus relative to previous babies

Birthweight difference between present baby and previous baby (kg)	Mother's opinion of size of fetus relative to previous baby			
	Smaller (*n* = 28)	Same (*n* = 57)	Larger (*n* = 55)	All women (*n* = 140)
−1·25 to −0·75	4 (14%)	2 (4%)	1 (2%)	7 (5%)
−0·75 to −0·25	9 (32%)	6 (11%)	4 (7%)	18 (13%)
−0·25 to +0·25	9 (32%)	27 (47%)	21 (38%)	56 (40%)
+0·25 to +0·75	6 (21%)	21 (37%)	20 (36%)	49 (35%)
+0·75 to +1·25	0	1 (2%)	8 (15%)	9 (6%)
+1·25 to +1·75	0	0	1 (2%)	1 (1%)
Mean of birthweight differences	−0·22	+0·14	+0·30	+0·13
SD	0·388	0·383	0·474	0·456
Significance of difference in birthweight between pregnancies				
t	2·99	2·71	4·70	
P	<0·01	<0·01	<0·001	
Significance of difference between mean birthweight differences compared with 'Same' group				
t	4·05		2·01	
P	<0·001		<0·05	

Table 2. Differences in birthweights between study and previous pregnancies in relation to mother's impression of size of fetus relative to previous baby

Differences in size of present baby relative to previous baby	Mother's opinion of size of fetus relative to previous baby			
	Smaller	Same	Larger	Total
Lighter	17 (61%)	19 (33%)	14 (25%)	50 (36%)
Heavier	11 (39%)	38 (67%)	41 (75%)	90 (64%)
Total	28	57	55	140

0·30 kg heavier than their previous babies, and the women who thought their babies would be smaller gave birth to babies which were on average 0·22 kg lighter than their previous babies. The total group in the study had babies which were on average 0·13 kg heavier than their previous babies. The distributions of birthweight differences in the groups who thought their babies would be larger and smaller were significantly different from those who estimated their babies to be the same size. The women who thought that their babies would be about the same size had babies which were on average 0·14 kg heavier than their previous babies (Table 1).

Of the 55 women who thought their baby would be larger, 41 (75%) had heavier babies than in the previous pregnancy. Of the 28 women who thought their babies would be smaller, 17 (61%) gave birth to lighter babies. In the total group studied, 90 (64%) of babies were heavier and 50 (36%) were lighter than the previous babies (Table 2).

Of the 57 women who thought their babies would be about the same size as their previous babies, 43 (75%) had babies with birthweights within 0·5 kg of the previous babies' birthweight; 92 (66%) of the total study group had babies with birthweights within 0·5 kg of that of their previous babies.

Table 3. Sensitivity, specificity and predictive values of maternal impressions of size of fetus relative to previous baby

	Mother's impression of size of fetus relative to previous baby	
	Smaller	Larger
Sensitivity	17/50 (34%)	41/90 (46%)
Specificity	79/90 (88%)	38/50 (76%)
Positive predictive value	17/28 (61%)	41/55 (75%)
Negative predictive value	79/112 (71%)	38/85 (45%)

Discussion

These results confirm a significant relation between the mother's impression of the relative size of her fetus compared to her previous baby and the actual difference in birthweights of the two babies.

The sensitivity of the mother's predictions of relative fetal size, however, is too low to be of any use as an isolated test of relative fetal size in clinical practice (Table 3) (Stempel 1982), but may have a role in combination with other established methods.

Abdominal palpation can estimate birthweight to within 1 pound (0·45 kg) in 79% of cases (Loeffler 1967). Of the 57 women who estimated that their babies would be about the same size as their previous babies, 76% had babies with birthweights within 0·5 kg of their previous babies' birthweights. Maternal estimation of relative fetal size should therefore be able to produce similar results to abdominal palpation.

Ultrasound can estimate fetal weight more precisely (Campbell & Wilkin 1975) and serial ultrasound measurement of fetal biparietal diameter and abdominal circumference is the most effective method of screening for SGA babies (Neilson *et al.* 1984). However, in many obstetric units this method is not routinely available to all women and individuals are selected for ultrasound scanning on the basis of abdominal palpation or symphysis fundal height measurements. The sensitivity of these techniques is much lower than ultrasound and thus a large number of SGA babies remain undetected (Hall *et al.* 1980; Persson *et al.* 1986). A larger study would be required to assess the effectiveness of maternal impression of fetal size in identifying SGA babies although the sensitivity and the positive predictive value suggest that it would be no better than other methods.

Bakketeig & Hoffman (1983) have demonstrated that similarity in birthweight between successive pregnancies in the same woman has a significant association with lower perinatal mortality. Determination of relative fetal size between pregnancies should therefore be as important as determination of actual fetal size and it is possibly in this area that the maternal impression of relative fetal size has most to offer.

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References

Altman, D G. & Coles, E. C. (1980) Nomograms for precise determination of birthweight for dates *Br J Obstet Gynaecol* **87**, 81-86.

Bakketeig, L S & Hoffman, H. J. (1983) The tendency to repeat gestational age and birthweight in successive births related to perinatal survival *Acta Obstet Gynaecol Scand* **62**, 385-392.

Campbell, S & Wilkin, D. (1975) Ultrasonic measurement of fetal abdomen circumference in the estimation of fetal weight. *Br J Obstet Gynaecol* **82**, 689-697.

Hall, M. H., Chng, P. K. & MacGillivray, I. (1980) Is routine antenatal care worthwhile? *Lancet* **ii**, 78-80.

Loeffler, F. E. (1967) Clinical fetal weight prediction *J Obstet Gynaecol Br Commonw* **74**, 675-677.

Neilson, J. P , Munjana, S P & Whitfield, C. R (1984) Screening for small-for-dates fetuses: a controlled trial. *Br Med J* **289**, 1179-1181.

Persson, B., Stangenberg, M , Lunell, N. O., Brodin, U., Holmberg, N. G. & Vaclavinkova, V. (1986) Prediction of size of infants at birth by measurement of symphysis fundal height. *Br J Obstet Gynaecol* **93**, 206-211.

Stempel, L. E (1982) Eenie, meenie, minie, mo . . . What do the data really show? *Am J Obstet Gynecol* **144**, 745-752.

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Decrease in pulsatile flow in the internal carotid artery in fetal hydrocephalus

S. DEGANI, R. LEWINSKY, I. SHAPIRO, M. SHARF

Summary. The effect of ventriculomegaly on pulsatile flow in the internal carotid arteries has been studied by Doppler ultrasound in four hydrocephalic fetuses. The pulsatility index showed progressive elevation proportional to the developing ventriculomegaly and thus may be a valuable index for the study of the mechanism of brain injury and for the determination of optimal timing of intervention.

Several environmental and genetic causes for hydrocephalus are known, but many cases are of unknown origin.

Intrauterine infection such as toxoplasmosis and cytomegalovirus infection may result in fetal hydrocephalus (Warkany *et al.* 1981). Stenosis of the aqueduct of Sylvius may occur as an X-linked recessive condition, and autosomal recessive inheritance of the Dandy–Walker syndrome has been reported (Warkany *et al.* 1981; Burton 1979). A number of chromosomal and mendelian disorders produce patterns of multiple anomalies that include hydrocephalus.

Although brain injury is related in part to the underlying disorder responsible for the hydrocephalus, ventricular dilatation *per se* may cause cerebral injury due to direct compression (Weller & Schulman 1972; Rubin *et al.* 1976; Fishman & Greer 1963) or to vascular compromise (Wozniak *et al.* 1975).

This report assesses the effect of ventriculomegaly on pulsatile flow in the fetal intracranial internal carotid artery.

Subjects and methods

A combined mechanical sector and pulsed Doppler system (Aloka SSD-730) with carrier frequency of 3·5 MHz was used for blood flow velocity measurements in the fetal internal carotid artery in four pregnancies complicated by fetal hydrocephalus, first diagnosed between 24 and 33 weeks of pregnancy, with progressive ventriculomegaly.

Using the method described previously (Wladimiroff *et al.* 1986), the maximum flow velocity waveform in the internal carotid artery was obtained at the level of the bifurcation into the middle and anterior cerebral artery. The sample size of the Doppler probe was 4 mm, allowing clear signals from the artery without interference from nearby vessels. The maximum flow velocity waveforms in the umbilical artery were recorded according to the method first described by McCallum *et al.* (1978).

The degree of pulsatility of the waveforms was quantified by calculating the pulsatility index (Gosling & King 1975) over at least four consecutive cardiac cycles. All the measurements were performed in the semi-recumbent position and during fetal apnoea, since high amplitude fetal breathing modulates the blood flow velocity waveforms.

Results

Table 1 summarizes the findings and pregnancy outcome in the four patients.

Level II sonographic assessment was made following the diagnosis of fetal ventriculomegaly

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Department of Obstetrics and Gynecology, Haifa Medical Center (Rothschild), Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel
S. DEGANI
R LEWINSKY
I. SHAPIRO
M SHARF

Correspondence: Dr S. Degani, Department of Obstetrics and Gynecology, Ultrasound Unit, Haifa City Medical Center (Rothschild), PO Box 4940, Haifa 31048, Israel

Table 1. Sonographic findings and pregnancy outcome

Patient no	Gestational age at diagnosis (weeks)	Indication for level I sonography	Interpretation of level II sonographic findings	Pregnancy outcome
1	24	Size/date discrepancy, twin pregnancy with one twin hydrocephalic	Hydrocephalus; LV/H = 75% (normal 23–33%) Cerebral mantle = 1·1 cm. Lumbo-sacral spina bifida, meningomyelocele	Term delivery Twin 1: normal female infant, twin 2: hydrocephalus + lumbar meningomyelocele, no other anomalies
2	33	Routine screening	Hydrocephalus; LV/H = 85% (normal 25–37%). Cerebral mantle = 1·3 cm. Lumbo-sacral spina bifida?	Elective termination; female fetus, hydrocephalus; Arnold-Chiari malformation; lumbar meningomyelocele
3	29	Routine screening	Hydrocephalus, LV/H = 69% (normal 22–37%) Cerebral mantle = 0 9 cm.	Elective termination, male fetus, isolated hydrocephalus
4	27	Rule out polyhydramnios	Hydrocephalus, LV/H = 73% (normal 23–34%), enlarged third ventricle. Cerebral mantle = 0·7 cm Polyhydramnios	Elective termination; male fetus; atresia of aqueduct of Sylvius; no other anomalies noted

LV/H, Lateral ventricle/hemispheric ratio.

by sonography performed for routine obstetric indications.

Individual pulsatility index values in the four patients with fetal hydrocephalus are illustrated in Fig. 1 together with the nomogram for the internal carotid artery (PI-ICA).

Pulsatility indices of the umbilical artery blood flow waveforms were all within normal limits.

The last measurements in all the patients indicated an absence of advancing blood flow in the internal carotid artery during diastole. The Pourcelot's index of resistance (Pourcelot 1974) had a maximal value of 1·00 (i.e. when $D = 0$ in the equation $\frac{S-D}{S}$.

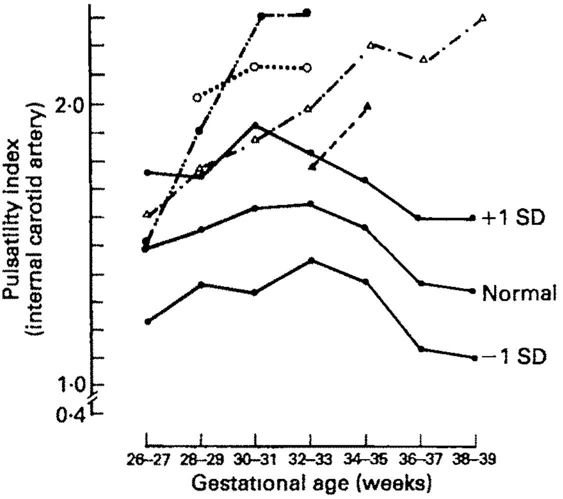

Fig. 1. Pulsatility index values of the internal carotid artery in four hydrocephalic fetuses. The mean ± 1 SD values of the normal range are shown. △— · —△, Case no. 1; ▲---▲, case no 2; ○ . . ○, case no. 3; ● ····●, case no. 4.

Discussion

In adults the brain, spinal cord and spinal fluid are encased, along with the cerebral vessels, in a rigid bony case. Because brain tissue and spinal fluid are essentially incompressible, the volume of blood, spinal fluid and brain in the cranium at any time must be relatively constant (Monro-Kellie doctrine) (Adams & Victor 1985). During fetal life the fontanelles and the open skull sutures enable better adaptation to increased intracranial volume.

The data presented in this report demonstrate an inverse relation between marked ventriculomegaly and pulsatile flow in the fetal internal carotid artery. The four patients each had an elevated pulsatility index because of a sharp decrease and, later, total cessation of blood flow during diastole.

In the absence of data relating the direct measurement of cerebral blood flow to the pulsatility index, this effect of ventriculomegaly cannot be quantified more precisely.

The cerebral circulation, unlike the peripheral circulation, has an important diastolic component to blood flow; our data indicate that there is a critical ventricular size beyond which there may be compromise of flow in the internal carotid artery. More data are needed to define the size in a more quantitative fashion.

The mechanism by which ventriculomegaly might lead to diminished blood flow in the cerebral arteries is most probably related to their stretching, or compression by the enlarged ventricle; Hill & Volpe (1982) found the ventriculomegaly to be a more critical factor than the intracranial pressure in the pathogenesis of the impaired flow in infantile hydrocephalus.

Experimental studies also demonstrate an adverse effect of ventriculomegaly on cerebral blood flow apparently by displacement, deformation, stretching and decrease in calibre of cerebral arteries and a dilatation of cerebral vessels after ventricular drainage (Wozniak *et al.* 1975). Compression of the fetal internal carotid artery by the dilated ventricles against the bony base of the skull is a possible mechanism leading to decrease in pulsatile flow.

A decision as to appropriate management of the pregnancy should be based on the stage of gestation at the time of diagnosis, the degree of ventricular dilatation and cerebral mantle compression, and the presence or absence of detectable associated anomalies (Harrison *et al.* 1981).

Compromised flow in the internal carotid artery may prove to be a sensitive barometer of impending brain ischaemic injury, so that determination of the pulsatility index may prove valuable in determining optimal timing for corrective intervention.

References

Adams, R. D. & Victor, M. (1985) *Principles of Neurology*, 3rd edn, McGraw-Hill Book Company, New York, p 463

Burton, B K. (1979) Recurrence risk for congenital hydrocephalus. *Clin Genet* **16**, 47-53.

Fishman, R. A. & Greer, M. (1963) Experimental obstructive hydrocephalus: changes in the cerebrum. *Arch Neurol* **8,** 156-161.

Gosling, R. G. & King, D. H. (1975) *Ultrasound Angiology, Arteries and Veins* (Marcus, A. W. & Adamson, L., eds), Churchill Livingstone, Edinburgh, pp. 61-98.

Harrison, M. R., Golbus, M. S. & Filly, R. A. (1981) Management of the fetus with a correctable congenital defect. *JAMA* **246,** 774-777.

Hill, A. & Volpe, J J. (1982) Decrease in pulsatile flow in the anterior cerebral arteries in infantile hydrocephalus. *Pediatrics* **69,** 4-7.

McCallum, W O., Williams, C. S., Hapel, S. & Daigle, R. E. (1978) Fetal blood velocity waveforms. *Am J Obstet Gynecol* **132,** 425-429.

Pourcelot, L. (1974) Applications cliniques de l'examen Doppler transcutane. In *Velocimétrie Ultrasonore Doppler* (Peronneau, P., ed.), Institut National de la Santé et de la Recherche Medicale, Paris, p. 213-240.

Rubin, R. C., Hochwald, G. M., Teill, M., Cooper, P. R. & Jacobs, G B. (1976) Hydrocephalus. I Histological and ultrastructural changes in the pre-shunted cortical mantle *Surg Neurol* **5,** 109-115.

Warkany, J., Lemire, R. J. & Cohen, M. M (1981) Hydrocephaly. In *Mental Retardation and Congenital Malformations of the Central Nervous System.* Year Book, Chicago, pp 48-82.

Weller, R. O. & Schulman, K (1972) Infantile hydrocephalus: clinical, histological and ultrastructural study of brain damage. *J Neurosurg* **36,** 255-265.

Wladimiroff, J. W., Tonge, H. M. & Stewart, P. A. (1986) Doppler ultrasound assessment of cerebral blood flow in human fetus. *Br J Obstet Gynaecol* **93,** 471-475.

Wozniak, M., McLane, D. G. & Raimondi, A. J. (1975) Micro- and macro-vascular changes as the direct cause of congenital murine hydrocephalus. *J Neurosurg* **43,** 535-545.

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The effect of vaginal delivery on the urethral sphincter

ANDREW TAPP, LINDA CARDOZO, EBOO VERSI,
JULIA MONTGOMERY, JOHN STUDD

Summary. To investigate the aetiological role of vaginal delivery in genuine stress incontinence we compared two groups of women who underwent full urodynamic assessment in our department. The women in the first group had competent urethral sphincter mechanisms and those in the second group had genuine stress incontinence. There were no differences between the two groups in respect of parity, number of vaginal deliveries or birthweight of the heaviest baby. The group with competent urethral sphincter mechanisms did show some evidence to implicate an increased number of vaginal deliveries in poor function of the distal part of the urethral sphincter mechanism.

Genuine stress incontinence is the most common cause of female urinary incontinence and has traditionally been associated with pregnancy, vaginal delivery, previous incontinence surgery, congenital weakness and the menopause. Thomas (1984) found that the prevalence of stress incontinence increased with increasing parity. Recent corroborative evidence that vaginal delivery may be an important aetiological factor has been provided by investigations of urethral and anal sphincter electrophysiology, and urethral pressure measurements.

Patients with genuine stress incontinence have abnormal conduction in the perineal branch of the pudendal nerve which innervates the periurethral striated muscle (Snooks *et al.* 1985*a*). Injury to the nerve supply of the pelvis may occur at childbirth and the pudendal nerve terminal motor latency is prolonged 48–72 h after vaginal delivery (Snooks *et al.* 1984, 1985*b*).

Urethral pressure studies have also shown that vaginal delivery may adversely affect urethral function. Vaginal delivery is associated with a reduction of the functional urethral length, urethral closure pressure and maximum urethral pressure (van Geelen *et al.* 1982). There is no change in these variables in women delivered by caesarean section.

In contrast to these findings there is considerable epidemiological evidence that implicates inherent urethral sphincter weakness and pregnancy *per se* in the genesis of genuine stress incontinence. Francis (1960) found that 53% of primigravidae complained of incontinence during pregnancy and 43% had suffered stress incontinence throughout their lives. None of her patients developed stress incontinence *de novo* postpartum and 91% of those who were incontinent during pregnancy improved in the puerperium. Beck & Hsu (1965) found that 64·5% of their stress incontinent patients first complained of incontinence when pregnant and 14·1% developed incontinence in the puerperium.

Thus, there appears to be conflicting evidence regarding the importance of vaginal delivery in

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Urodynamic Unit, Department of Obstetrics and Gynaecology, King's College Hospital, Denmark Hill, London SE5
ANDREW TAPP *Research Registrar*
LINDA CARDOZO *Consultant*
EBOO VERSI *Registrar*

Menopause Clinic, Department of Obstetrics and Gynaecology, Dulwich Hospital, East Dulwich Grove, London SE22
JULIA MONTGOMERY *Research Registrar*
JOHN STUDD *Consultant*

Correspondence: A Tapp, Registrar, Department of Obstetrics and Gynaecology, Greenwich District Hospital, Vanbrugh Hill, London SE10 9HE

the subsequent development of stress incontinence. We performed a retrospective study comparing continent women with incontinent women in order to investigate the effect of childbirth on the subsequent integrity of the urethral sphincter mechanism.

Patients and methods

Two groups of women were recruited for this study. Group 1 presented to a gynaecological clinic with a variety of gynaecological problems but did not have primary urological complaints. This group was investigated as part of a study into the prevalence of lower urinary tract symptoms and urodynamic abnormalities in a 'normal' population. They were shown, by absence of leakage of contrast medium per urethram at videocystourethrography, to have competent urethral sphincter mechanisms. Group 2 were patients recruited from a urodynamic clinic complaining of incontinence and all had genuine stress incontinence proven by leakage of contrast medium per urethram at videocystourethrography. Both groups had a full gynaecological and urological history taken and were examined to exclude gynaecological abnormalities. Each patient completed a detailed urological symptom questionnaire. Details of parity, number of vaginal deliveries and birthweight of the heaviest baby were sought.

Ethics committee approval was given for this study and all the women gave informed consent. All patients were investigated by uroflowmetry and videocystourethrography (Bates *et al.* 1970). Urethral pressure profilometry was performed as described by Hilton & Stanton (1983) using a Gaeltec 7 French catheter with two depressed solid-state microtransducers mounted 6 cm apart. All recordings were taken with the patient supine and with 250 ml of normal physiological saline instilled into the bladder. The orientation of the transducers was lateral (9 o'clock). Reproducible resting and stress profiles were obtained using a constant speed withdrawal device to retract the catheter through the urethra at a speed of 2·5 mm/s. Measurements were also taken with the urethral transducer at the maximum urethral pressure for 2 min whilst the patient and catheter were watched for movement. In all, 31 variables of the urethral pressure profile were analysed. The investigation of both groups was carried out by the same observers using the same methods.

All the information obtained was computerized and the Statistical Package for Social Sciences (SPSS) was used for analysis. The Mann–Whitney *U*-test was used for the comparison of groups and Spearman's rank correlation coefficient for all correlations.

Results

Group 1 consisted of 148 women (mean age 50·1 years) and group 2 of 89 patients (mean age 51·6 years). There were no statistically significant differences in mean age, menopausal age, ponderal index and birthweight of the heaviest baby between the two groups (Table 1). There were also no significant differences in parity and number of vaginal deliveries between the two groups (Table 2). We performed multiple regression analysis controlling for age, menopausal age and ponderal index and tested the difference between the groups for parity, number of vaginal deliveries and birthweight of the heaviest baby and again found no difference.

Number of vaginal deliveries

In the women with competent urethral sphincter mechanisms (group 1) there were significant negative correlations between the resting ($P = 0{\cdot}02$) and stress ($P = 0{\cdot}04$) areas under the curve distal to the point of maximal urethral pressure and the number of vaginal deliveries (Table 3). There was a significant positive correlation ($P = 0{\cdot}02$) between transmission pressure ratios in the proximal 1/4 of the urethra (Q_1) and the number of vaginal deliveries and a negative correlation ($P = 0{\cdot}03$) in the distal 1/4 of the urethra (Q_4) (Table 3).

When investigating distal urethral function using urethral pressure profilometry the most important variables are the areas under the resting and stress profiles distal to the maximum urethral pressure and the transmission of intra-abdominal pressure to the distal urethra. The implication here is that an increasing number of vaginal deliveries is associated with poorer function of the distal urethra but there is, perhaps, proximal compensation. It would be inappropriate to carry out similar statistical analysis for women with genuine stress incontinence as the urethral pressure profile does not reflect the severity of the stress incontinence.

Table 1. Comparison of age, menopausal age, ponderal index, and birthweight of the heaviest baby between those with competent urethral sphincter mechanisms (group 1) and those with incompetent urethral sphincter mechanisms (group 2)

	Group 1			Group 2		
	n	Mean	(SD)	*n*	Mean	(SD)
Age (years)	148	50·1	(6·02)	89	51·6	(8·78)
Menopausal age (years)	148	2·52	(4·03)	89	3·41	(6·61)
Ponderal index*	128	0·25	(0·044)	66	0·26	(0·046)
Nulliparae	19			22		
Heaviest birthweight (g)†	112	3·66	(0·58)	52	3·47	(0·84))

* Data missing for 20 women in group 1 and 23 in group 2 † Seventeen women in group 1 and 15 in group 2 were unsure of birthweights Mann–Whitney *U*-test.

Table 2. Median number of vaginal deliveries in women with competent (group 1) and incompetent (group 2) urethral sphincter mechanisms

	Group 1 (*n* = 144)	Group 2 (*n* = 80)
	Median (5th–95th centile)	Median (5th–95th centile)
Parity	3 (0–6)	2 (0–7)
Vaginal deliveries	2 (0–5)	2 (0–7)

Data missing for four women in group 1 and nine women in group 2 Mann–Whitney *U*-test.

Table 3. Correlation between urethral pressure profile (UPP) measurements and number of vaginal deliveries and birthweight of the heaviest baby in women with competent urethral sphincter mechanisms (group 1)

	Spearman's rank correlation coefficient for	
UPP measurements	No. of vaginal deliveries (*n* = 144)	Birthweight (*n* = 112)
Resting profile		
Total area	−0·085	−0·133
Area to peak	0·049	−0·07
Area after peak	−0·189*	−0·138
Length to peak	0·139	0·104
Functional urethral length	−0·098	0·104
Total profile length	−0·123	0·055
Closure pressure	−0·018	−0·242*
Maximum urethral pressure	−0·038	−0·217*
Stress profile		
Total area	−0·067	−0·049
Area to peak	−0·014	−0·040
Area after peak	−0·153*	−0·132
Length to peak	0·016	0·104
Functional urethral length	−0·136	0·004
Closure pressure	−0·037	−0·154
Transmission pressure ratios†		
Q_1	0·174*	0·058
Q_2	0·089	−0·011
Q_3	−0·078	−0·029
Q_4	−0·163*	−0·032

* $P<0·05$ † Functional urethral length divided into quarters Proximal to distal.

Birthweight of heaviest baby

In group 1 there were significant negative correlations between birthweight of the heaviest baby and resting maximum urethral pressure and urethral closure pressure. There were no significant correlations between birthweight and transmission pressure ratios (Table 3).

Discussion

Women with genuine stress incontinence have evidence of damage to the perineal branch of the pudendal nerve (Snooks *et al.* 1985*a*) which supplies the periurethral striated muscle. Injury to the nerve supply of the pelvis may occur at childbirth and is manifested by abnormal pudendal nerve terminal motor latencies. Multiparity and instrumental delivery have been identified as obstetric risk factors which may compound the peripheral nerve damage (Snooks *et al.* 1984, 1985*b*). In women delivered by caesarean section, however, there is no change in pudendal nerve terminal motor latencies after delivery Two months after vaginal delivery the prolonged conduction time of the pudendal nerve tends to return to normal, but the fibre density of the external anal sphincter remains abnormal Other obstetric factors which have been implicated in the genesis of pudendal nerve damage are: the length of the second stage of labour in primiparous patients and the birthweight of the baby. Therefore, it is postulated, that pudendal nerve damage, as a consequence of a variety of factors occurring around the time of delivery, may be important in the aetiology of genuine stress incontinence.

Van Geelen *et al.* (1982) felt that changes in the features of the urethral pressure profile which were seen postpartum resulted solely as a consequence of the fetus passing through the birth canal and concluded that other delivery factors were of minor importance. Pregnancy itself does not appear adversely to affect urethral function (van Geelen *et al.* 1982; Iosif *et al.* 1980).

To add further confusion to the arguments surrounding the influence of vaginal delivery on the urethral sphincter mechanism, Corcoran *et al.* (1986) could find no correlation between electrophysiological evidence of sphincter denervation and the urethral pressure profile Therefore, doubt has been thrown on the functional significance of pelvic denervation occurring as a consequence of vaginal delivery. It should be noted, however, that their techniques were different from those described by Snooks *et al.* (1984, 1985 *a*, *b*).

In our study an increasing number of vaginal deliveries has some association with adverse changes to the urethral pressure variables that reflect distal urethral function. The periurethral striated muscle has an occlusive action on the female urethra distal to the maximum urethral pressure (Gosling 1984). Therefore, vaginal delivery may well result in impairment of the function of this muscle. One may speculate that our results are compatible with those of Snooks *et al.* (1985*a*) as the perineal branch of the pudendal nerve supplies the periurethral striated muscle.

The significance of any damage to the distal part of the urethral sphincter mechanism is unclear. Traditionally it has been taught that urine is held at the bladder neck (Ellis 1972), but we have shown that 50% of continent climacteric women have an open bladder neck in response to a raised intra-abdominal pressure (Versi *et al.* 1986). If this were also true for women of reproductive age, then damage to the distal part of the urethral sphincter as a result of vaginal delivery would be of considerable importance in the maintenance of continence.

Genuine stress incontinence has a number of causes and it would be simplistic to implicate one element alone. We found that women with genuine stress incontinence, when matched for age, menopausal age and ponderal index, had the same number of vaginal deliveries as a continent control group. Yet, in the control group vaginal delivery appeared to result in some distal sphincter impairment. We therefore speculate that there is an 'at risk' population and damage to the distal sphincter mechanism, which may occur as a consequence of vaginal delivery, compromises poor proximal function and may result in incontinence.

References

Bates, C P , Whiteside, C G & Turner-Warwick, R (1970) Synchronous cine-pressure-flow-cysto-urethrography with special reference to stress and urge incontinence. *Br J Urol* **42,** 714-723

Beck, R. P. & Hsu, N. (1965) Pregnancy, childbirth and the menopause related to the development of stress incontinence *Am J Obstet Gynecol* **91,** 820-823

Corcoran, M., Brown, A. D. G , McInnes, A. & Chisholm, G. D. (1986) Urethral sphincter function and denervation in genuine stress incontinence. 24th British Congress of Obstetrics and Gynaecology Cardiff. Abstract 114

Ellis, H. (1972) *Clinical Anatomy*, 5th edn. Blackwell Scientific Publications, Oxford

Francis, W. J. A (1960) The onset of stress incontinence. *J Obstet Gynaecol Br Emp* **67**, 399-903.

van Geelen, J M., Lemmens, W. A. J. G , Eskes, T K A B. & Martin, C. B. (1982) The urethral pressure profile in pregnancy and after delivery in healthy nulliparous women. *Am J Obstet Gynecol* **144**, 636-649

Gosling, J. A (1984) Anatomy. In *Clinical Gynecological Urology*, 1st edn, (Stanton, S L , ed.), C V Mosby, St Louis, pp. 3-12.

Hilton, P. & Stanton, S. L. (1983) Urethral pressure measurements by microtransducer; the results in symptom-free women and in those with genuine stress incontinence. *Br J Obstet Gynaecol* **90**, 919-933.

Iosif, S , Ingermarsson, I & Ulmsten, U (1980) Urodynamic studies in normal pregnancy and the puerperium. *Am J Obstet Gynecol* **137**, 696-700.

Snooks, S. J., Swash, M., Setchell, M. & Henry, M. M (1984) Injury to the innervation of pelvic floor sphincter musculature in childbirth. *Lancet* **ii**, 546-550

Snooks, S. J., Badenoch, D F., Tiptaft, R C. & Swash, M (1985*a*) Perineal nerve damage in genuine stress incontinence An electrophysiological study *Br J Urol* **57**, 422-426

Snooks, S. J , Swash, M , Henry, M M. & Setchell, M (1985*b*) Risk factors in childbirth causing damage to the pelvic floor innervation *Br J Surg* **72**, S15-17.

Thomas, T M (1984) Epidemiology of micturition disorders. In *Clinical Gynaecological Urology*, 1st edn, (Stanton, S. L , ed.), C V. Mosby, St Louis, pp. 35-42

Versi, E., Cardozo, L. D., Studd, J W. W., Brincat, M , O'Dowd, T M & Cooper, D. (1986) The internal urinary sphincter in maintenance of female continence. *Br Med J* **292**, 166-167

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Correlation of urethral physiology and skin collagen in postmenopausal women

EBOO VERSI, LINDA CARDOZO, MARK BRINCAT,
DEREK COOPER, JULIA MONTGOMERY, JOHN STUDD

Summary. Connective tissue collagen is thought to contribute to the generation of urethral pressure. It has been previously shown that skin collagen and urethral pressure are oestrogen dependent. This study demonstrates a correlation between urethral pressure measurements and skin collagen content. It is suggested that the beneficial effect of oestrogens on urethral function may be mediated by collagen.

The prevalence of incontinence increases with age (Thomas *et al.* 1980), and around the time of the menopause genuine stress incontinence is the most common primary pathology (Bent *et al.* 1983). As continence is maintained by urethral pressure exceeding bladder pressure (Enhorning 1961), a study of urethral pressure is fundamental to the understanding of continence mechanisms (Assmussen & Ulmsten 1975). Connective tissue elements have been implicated in the functional properties of the urethra (Gosling 1979) and as collagen is a major component of connective tissue, it would seem reasonable to postulate that urethral collagen may contribute to the generation of the urethral pressure profile (UPP).

A study examining the relation between urethral collagen and urethral pressures should ideally involve the measurement of urethral collagen. Unfortunately this would involve taking urethral biopsies, a procedure that would be difficult to justify on ethical grounds. For this reason we have used skin collagen as our model for urethral collagen.

About 90% of all the collagen in the body is type I (Alberts *et al.* 1983) and structural collagen in the urethra is probably of the same type as that in skin, namely types I and III. We have shown that skin collagen content and skin thickness decline after the menopause (Brincat *et al.* 1985, 1987) but can be restored following oestrogen replacement therapy (Brincat *et al.* 1983, 1985). It is therefore possible that increases in urethral pressure noted after hormone replacement therapy (Faber & Heidenreich 1977; Walters *et al.* 1978; Rud 1980*a*; Hilton & Stanton 1983*b*; Beisland *et al.* 1984) are a product of the actions of oestrogens on urethral collagen.

Skin thickness reflects general connective tissue status and collagen is a component of this (Brincat *et al.* 1985). However, skin thickness also depends upon the hydration of the skin, a feature that is largely independent of the collagen effect To examine the relation between urethral pressure and skin collagen and thickness a correlation analysis has been performed between the urethral pressure profile variables and skin collagen content and thickness measurements

Patients and methods

Patient recruitment was from the Dulwich menopause clinic. These patients had presented

Urodynamic Unit, King's College Hospital and Dulwich Menopause Clinic, London
EBOO VERSI
LINDA CARDOZO
MARK BRINCAT
JULIA MONTGOMERY
JOHN STUDD

Computer Unit, King's College Hospital School of Medicine and Dentistry, London University, London
DEREK COOPER

Correspondence. Linda Cardozo, MD, MRCOG, King's College Hospital, Denmark Hill, London SE5 9RS

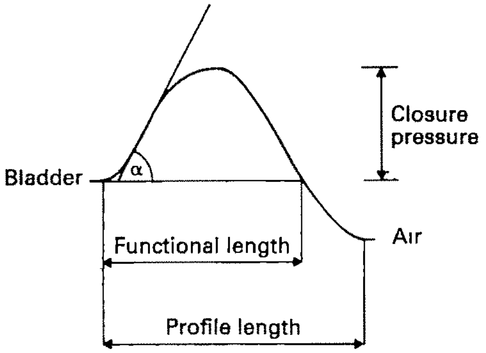

Fig. 1. Urethral pressure profile at rest Skin collagen content was significantly correlated with profile length ($P<0{\cdot}02$) and the angle α ($P<0{\cdot}02$).

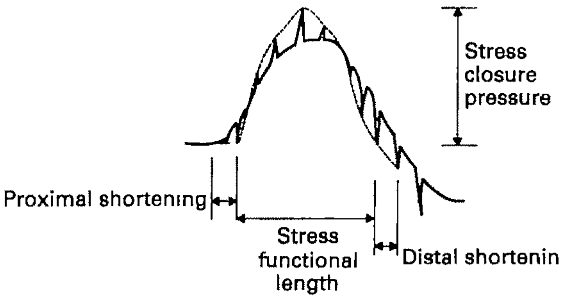

Fig. 2. Variables of the stress profile as shown on the subtraction trace Skin collagen content was significantly correlated with proximal shortening ($P<0{\cdot}01$), stress functional length ($P<0{\cdot}05$) and stress closure pressure ($P<0{\cdot}05$).

to the clinic complaining of climacteric symptoms which were predominantly vasomotor in nature None of the patients had received hormone replacement therapy nor had any patient undergone bladder neck surgery for incontinence or prolapse but about a third had previously had a hysterectomy for other benign gynaecological conditions.

A full gynaecological and urological history was taken and all the women had a general gynaecological examination to ensure that the study group consisted of normal healthy women All patients had a 3 mm full thickness skin biopsy taken from the right thigh for analysis of skin collagen content (Woessner 1961; Neuman & Logan 1950). Skin thickness of the forearm was assessed radiologically with the use of a modification of a technique described by Black (1975). These skin studies form a part of the menopause clinic screening process concerned with osteoporosis research (Brincat 1985).

Lower urinary tract symptomatology is a recognized aspect of the menopause syndrome and so the patients presenting to the clinic had their urine sent for microscopy and culture to exclude a urinary tract infection. Urodynamic assessment was attempted in 86 women but two were unable to complete the tests which consisted of a simple pad test (Versi & Cardozo 1986), uroflowmetry, videocystourethrography (Bates *et al.* 1970) and urethral pressure profilometry (Hilton & Stanton 1983*a*). A third of the women had urodynamic abnormalities and only 55 women had completely normal urodynamic assessment results; these 55 women formed the study group

They had a mean age of 51·4 (SD 7·4) years and a mean menopausal age of 4·7 (SD 6·7) years calculated as the time since the last menstrual period or from the onset of climacteric symptoms in patients who had previously had a hysterectomy.

All patients had high postmenopausal levels of serum gonadotrophins (FSH >40 i.u./l; LH >25 i.u./l) and low serum oestradiol levels (mean 156, SD 15; max 220 pmol/l).

The technique of urethral pressure profilometry was the same as that reported by Hilton & Stanton (1983*a*) using a Gaeltec 7 French catheter with two solid-state depressed transducers mounted 6 cm apart. Recordings were taken in the supine position with 250 ml of physiological saline in the bladder. The orientation of the transducers was lateral (9 o'clock). Recordings of resting (Fig. 1) and stress (Fig. 2) profiles were regarded as satisfactory if two consecutive profiles were the same. Measurements were also taken with the urethral sensor at the point of maximum urethral pressure

Measurement and analysis

Collagen content was measured indirectly by the amount of hydroxyproline in the sample as described by Woessner (1961). Skin samples were frozen (dry) and kept at −20°C before the assay The samples were thawed and homogenized in hydrochloric acid (6M) and then subjected to a chloramine T extraction procedure. Ehrlich's reagent was used to produce a colour reaction which was measured spectrophotometrically at 557 nm to estimate the amount of hydroxyproline. The collagen content was calculated with a transformation factor as

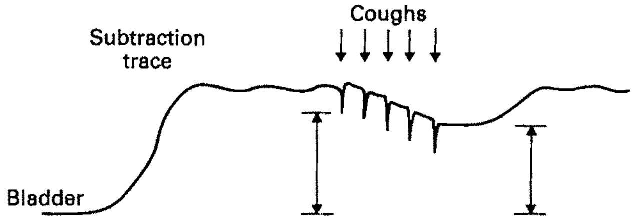

Fig. 3. Changes in maximum urethral pressure due to coughs; there was a significant correlation with skin collagen content ($P<0.05$)

described by Neuman & Logan (1950) and expressed in µg/mm^2 of skin. The intra- and interassay coefficients of variation were 11·4% and 9·8% respectively (Brincat 1985).

Figures 1 and 2 show the variables of the resting and stress pressure profiles that were recorded. The Hewlett-Packard digitizer was programmed to enable measurements of the areas under the resting and stress profiles to be measured. To estimate the rate of change of pressure in the proximal urethra, a regression line was fitted to the digitized points on the curve, proximal to the peak point. The gradient of this line was then used in the correlation analysis.

The response to a single cough and to six coughs (Fig. 3) was measured on the subtraction trace by noting the instantaneous minimum pressure during the cough, the sustained urethral closure pressure following the cough(s) and the recovery time to the maximum urethral pressure. Transmission pressure ratios as a measure of the differential transmission of the cough impulse to the urethra and bladder were calculated as shown in Fig. 4. For every subject the transmission pressure ratio of every cough in the stress profile was calculated and the maximum value was noted for each patient.

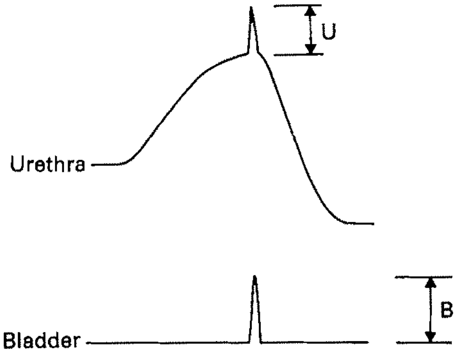

Fig. 4. Calculation of the transmission pressure ratio (TPR) from the urethral pressure profile TPR = U/B × 100

All the information was computerized and the SPSS was used to calculate the correlations between skin collagen content and thickness and the urethral pressure profile variables. The Kolmogorov–Smirnov test for normality was used to justify the use of Pearson's correlation analysis. Where the data were found to be non-parametric, Spearman's rho was calculated.

Wherever possible, the terms used have been in accordance with the recommendations of the Standardisation Committee of the International Continence Society.

Results

Table 1 gives the means and standard deviations of all the variables measured for the 55 women in this study and Table 2 gives the correlation coefficients and their significance levels tabulated for the measured urethral pressure variables and skin collagen content and skin thickness. Three women did not have urethral pressure stress profiles performed due to equipment failure. Two women did not have radiological assessment of their skin thickness and the results of four skin collagen assays were lost, two due to technical problems and two due to an error of administration.

Although only one urethral pressure variable correlated significantly with skin thickness, there were several significant correlations with skin collagen content.

At rest there were positive correlations between collagen and proximal urethral pressure measurements, this relation was not observed between skin thickness and resting pressures. There were significant correlations between all stress profile variables and collagen content. Proximal shortening reflects bladder neck incompetence (Versi *et al.* 1986) and this was negatively correlated with collagen content. Thus all four stress profile correlations indicated that collagen was positively correlated with sphincteric function. The only significant cor-

Table 1. Urethral pressure measurements, skin collagen content and skin thickness

Urethral pressure measurements	*n*	Mean (SD)
Resting profile		
Length to peak (mm)	55	11·9 (3·2)
Functional urethral length (mm)	55	29·2 (5·5)
Total profile length (mm)	55	34·2 (7·8)
Maximum urethral closure pressure (cm H_2O)	55	43·2 (17·5)
Pressure gradient in the proximal urethra	55	0·93 (0·23)
Area under resting profile (units)		
Before peak	55	67 (41)
After peak	55	124 (62)
Total area	55	193 (86)
Stress profile		
Proximal shortening (mm)	52	2·7 (4·3)
Length to peak (mm)	52	11·1 (4·8)
Functional length (mm)	52	20·3 (8·9)
Maximum closure pressure (cm H_2O)	52	59·2 (113·0)
Maximum transmission pressure ratio (%)	52	103 (23)
At maximum urethral pressure		
Response to a single cough		
Minimum pressure (cm H_2O)	52	29·3 (17·1)
Sustained pressure (cm H_2O)	52	32·5 (21·0)
Recovery time (s)	52	9·6 (9·2)
Response to six coughs		
Minimum pressure (cm H_2O)	52	16·1 (14·5)
Sustained pressure (cm H_2O)	52	26·0 (20·9)
Recovery time (s)	52	10·4 (6·7)
Thigh skin collagen content (μg/mm^2)	51	149 (48)
Forearm skin thickness (mm)	53	0·82 (0·13)

relation between skin thickness and the stress profile variables was a negative correlation with the ‘length to peak’.

Discussion

The results clearly demonstrate that there are numerous statistically significant correlations between thigh skin collagen content and various variables of the urethral pressure profile. The correlations do not only hold for the resting profile measurements but also for those during coughing (under stress). The only negative correlation was with proximal shortening. This phenomenon is seen in patients with an incompetent bladder neck (Versi *et al.* 1986) and the negative association with skin collagen content implies that the degree of bladder neck competence is positively correlated with collagen content Thus in all the variables studied, greater ‘sphincteric function’ was associated with greater collagen content of skin.

The variables of the stress profile were all significantly correlated with skin collagen content. This is a particularly important finding when it is understood that the stress profile is thought to reflect the competence of the urethral sphincter mechanism (Griffiths 1980). The stress profile is generated during coughing by subtracting the pressure in the bladder from that in the urethra. It is therefore a product of the relative forces exerted on the urethra and bladder. The latter can be examined by analysis of the transmission pressure ratio and so it is interesting to note that collagen was positively correlated with the maximum transmission pressure ratio (Fig. 4). In functional terms, the greater the latter quantity, the less likely is the possibility of stress incontinence.

Why the proximal area (Fig. 1) but not the distal or total area should be positively correlated with skin collagen content is not known. However, if urethral collagen is under similar genetic/hormonal control mechanisms as skin collagen, then it is tempting to speculate that urethral collagen contributes mainly to proximal urethral pressure at rest. During coughing, however, its influence would be more widespread but

Table 2. Correlations between urethral pressure measurements, skin collagen content and skin thickness

	Collagen content			Skin thickness		
Urethral pressure measurements	*n*	*r*	*P*	*n*	*r*	*P*
Resting profile						
Length to peak (mm)	51	+0·28	<0·05	53	−0·17	NS
Functional urethral length (mm)	51	+0·23	NS	53	−0·15	NS
Total profile length (mm)	51	+0·37	<0·02	53	−0·07	NS
Maximum urethral closure pressure (cm H_2O)	51	+0·20	NS	53	−0·02	NS
Pressure gradient in the proximal urethra	51	+0·36	<0·02	53	+0·15	NS
Area under resting profile (units)						
Before peak	51	+0·31	<0·05	53	−0·16	NS
After peak	51	+0·04	NS	53	−0·02	NS
Total area	51	+0·19	NS	53	−0·11	NS
Stress profile						
Proximal shortening (mm)	48	−0·44	<0·01	50	−0·08	NS
Length to peak (mm)	48	+0·32	<0·05	50	−0·33	<0·02
Functional length (mm)	48	+0·29	<0·05	50	−0·08	NS
Maximum closure pressure (cm H_2O)	48	+0·32	<0·05	50	−0·13	NS
Maximum transmission pressure ratio (%)	48	+0·45	<0·01	50	−0·09	NS
At maximum urethral pressure						
Response to single cough						
Minimum pressure (cm H_2O)	48	+0·30	<0·05	50	+0·09	NS
Sustained pressure (cm H_2O)	48	+0·22	NS	50	+0·12	NS
Recovery time (s)	48	−0·23	NS	50	+0·16	NS
Response to six coughs						
Minimum pressure (cm H_2O)	48	+0·25	NS	50	+0·06	NS
Sustained pressure (cm H_2O)	48	+0·33	<0·02	50	+0·22	NS
Recovery time (s)	48	−0·19	NS	50	−0·08	NS

NS, Not significant

specifically 'seen' as an effect on the maximum transmission pressure ratio.

Skin thickness and collagen content decline after the menopause (Brincat *et al.* 1983), and Rud (1980*b*) has shown that urethral pressure deteriorates with age. It is therefore possible that the correlations presented here (between collagen and urethral pressure profile variables) are merely spurious and just an effect of age. However, the fact that collagen content, rather than skin thickness, acts as a better correlate suggests that this is not merely an age-related phenomenon but that it is specifically collagen rather than general connective tissue status that is influential in the generation of urethral pressures. Further, it is interesting to note that collagen correlated positively with sphincteric function while the only significant correlation with skin thickness was negative.

Analysis of collagen is important because it appears to be oestrogen dependent. As skin collagen correlates with some aspects of urethral function, our hypothesis is that oestrogen-induced increase in skin collagen would also result in improved sphincteric function. This hypothesis can be readily tested by examining women after oestrogen replacement therapy.

The effect of the menopause on urethral function could therefore be monitored by analysis of skin changes. The effect of oestrogen on collagen metabolism may be directly mediated on fibroblasts or indirectly via other hormonal axes (e.g. growth hormone). In either case collagen may be the pivot through which oestrogens have their beneficial effect on sphincteric function (Hilton & Stanton 1983*b*).

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References

Alberts, B., Bray, D., Lewis, J., Raff, M., Roberts, K. & Watson, J. D. (1983) Cell-cell adhesions and the extra-cellular matrix In *Molecular Biology of the Cell* (Alberts, B., ed.), Garland Publishers, Inc , New York, London, pp 673-715.

Asmussen, M. & Ulmsten, U. (1975) Simultaneous urethrocystometry and urethra pressure profile measurement with a new technique *Acta Obstet Gynecol Scand* **54,** 385-386.

Bates, C P , Whiteside, C G. & Turner-Warwick, R (1970) Synchronous cine/pressure/flow/cysto-urethrography with special references to stress and urge incontinence. *Br J Urol* **42,** 714-723.

Beisland, H. O., Fossberg, E., Moer, A & Sander, S. (1984) Urethral sphincter insufficiency in postmenopausal females: treatment with phenylpropanolamine and estriol separately and in combination *Urol Int* **39,** 211-216

Bent, A. E., Richardson, D A. & Ostergard, D R (1983) Diagnosis of lower urinary tract disorder in postmenopausal patients *Am J Obstet Gynecol* **145,** 218-222.

Black, M M (1975) A modified radiographic method for measuring skin thickness *Br J Dermatol* **93,** 639-643.

Brincat, M. (1985) Skin collagen content and thickness and their relationship to bone in untreated and oestrogen treated postmenopausal women PhD Thesis, University of London

Brincat, M., Moniz, C F., Studd, J W. W , Darby, A J , Magos, A. L. & Cooper, D J. (1983) Sex hormones and skin collagen content in post-menopausal women. *Br Med J* **287,** 1337-1338.

Brincat, M., Moniz, C F , Studd, J. W. W., Darby, A. J., Magos, A L., Embrey, G & Versi, E (1985) The long term effects of the menopause and of administration of sex hormones on skin collagen and skin thickness *Br J Obstet Gynaecol* **92,** 256-259.

Brincat, M , Moniz, C. F., Kabalan, S., Versi, E., O'Dowd, T., Magos, A L., Montgomery, J. & Studd, J. W. W (1987) Decline in skin collagen content and metacarpal index at the menopause and its prevention with sex hormone replacement. *Br J Obstet Gynaecol* **94,** 126-129.

Enhorning, G. (1961) Simultaneous recording of intravesical and intraurethral pressure. A study on urethral closure in normal and stress incontinent women. *Acta Chir Scand* **276 (Suppl.),** 1-68

Faber, P. & Heidenreich, J. (1977) Treatment of stress incontinence with estrogen in postmenopausal women. *Urol Int* **32,** 221-223.

Gosling, J. A. (1979) The structure of the bladder and urethra in relation to function. *Urol Clin North Am* **6,** 31-38.

Griffiths, D. J (1980) *Urodynamics Medical Physics Handbooks 4* Adam Hilger Ltd, Bristol

Hilton, P & Stanton, S. L. (1983*a*) Urethral pressure measurements by microtransducer· the results in symptom-free women and in those with genuine stress incontinence. *Br J Obstet Gynaecol* **90,** 919-933

Hilton, P. & Stanton, S L (1983*b*) The use of intravaginal oestrogen cream in genuine stress incontinence *Br J Obstet Gynaecol* **90,** 940-944

Neuman, R. E. & Logan, M A. (1950) The determination of collagen and elastin in tissues. *J Biol Chem* **186,** 549-556

Rud, T (1980*a*) The effects of estrogens and gestagens on the urethral pressure profile in urinary continent and stress incontinent women. *Acta Obstet Gynecol Scand* **59,** 265-270.

Rud, T (1980*b*) Urethral pressure profile in continent women from childhood to old age *Acta Obstet Gynecol Scand* **59,** 331-335

Thomas, T M , Plymat, K R , Blannin, J. & Meade, T W. (1980) Prevalence of urinary incontinence. *Br Med J* **281,** 1243-1245.

Versi, E & Cardozo, L. D. (1986) Perineal pad weighing versus videographic analysis in genuine stress incontinence *Br J Obstet Gynaecol* **93,** 364-366

Versi, E , Cardozo, L. D , Studd, J. W. W., Brincat, M , O'Dowd, T M. & Cooper, D. J. (1986) Internal urinary sphincter in maintenance of female continence. *Br Med J* **292,** 166-167

Walters, S., Wolf, H., Barlebo, H. & Jensen, H K (1978) Urinary incontinence in postmenopausal women treated with estrogens A double blind clinical trial. *Urol Int* **33,** 136-143

Woessner, J. E Jr (1961) The determination of hydroxyproline in tissue and protein samples containing small proportions of this amnio acid *Arch Biochem Biophys* **93,** 440-447

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Clinical features of women with chronic lower abdominal pain and pelvic congestion

R. W. BEARD, P. W. REGINALD, JANE WADSWORTH

Summary. The clinical features of 35 women with pelvic pain and demonstrable congestion on pelvic venography have been characterized by comparing their symptoms and signs with those of 22 women with pelvic pain due to classical pathology. Women with pelvic pain and congestion had a mean age of 32·4 years, were more often multiparous and had had symptoms for 6 months to 20 years. The pain was dull and aching with sharp exacerbations. In individual women it commonly occurred on one side of the abdomen but unlike the pain due to 'classical pathology', it could occur on the other side. The pain was exacerbated by postural changes, and walking. Congestive dysmenorrhoea, deep dyspareunia and postcoital ache were common findings in women with pelvic congestion and 60% had evidence of significant emotional disturbance. The combination of tenderness on abdominal palpation over the ovarian point and a history of postcoital ache was 94% sensitive and 77% specific for discriminating pelvic congestion from other causes of pelvic pain.

Pelvic pain for which, until recently, no obvious somatic pathology could be found is a well known, frequent and poorly understood complaint in women of reproductive age (Renaer 1981). It leads to a variable interference with daily life ranging from occasional absence from work to serious marital disharmony. In its acute form, it may lead to emergency admission to hospital for suspected appendicitis or ectopic pregnancy. Despite wide-ranging studies which have been published over the last 150 years, the condition and its management have remained an enigma.

The classical studies by Taylor (1949*a*, *b*, *c*, 1954) in the USA and more recently by Renaer *et al.* (1980) have done much to characterize the condition but they fall short of convincingly demonstrating its cause and, of even greater importance, of proposing an effective form of treatment. Taylor's work was done at a time when investigative tools such as laparoscopy, pelvic venography and ultrasound were not available. In addition, many studies of this condition can be criticized because of poor design and the use of defective diagnostic methods which did not allow a satisfactory distinction between different causes of the pelvic pain.

An earlier laparoscopic study by Beard *et al.* (1984) showed that 91% of women complaining of chronic pelvic pain with no other pelvic pathology had dilated veins and vascular congestion in the broad ligaments and ovarian plexus.

The study reported here was designed to define the clinical features of women with pelvic congestion and to determine whether it is possible to distinguish them from those with other pelvic pathology.

St Mary's Hospital Medical School, London W2 1PG
Department of Obstetrics and Gynaecology
R. W. BEARD *Professor*
P. W. REGINALD *Lecturer/Senior Registrar*

Academic Department of Community Medicine
JANE WADSWORTH *Lecturer*

Correspondence: R. W. Beard

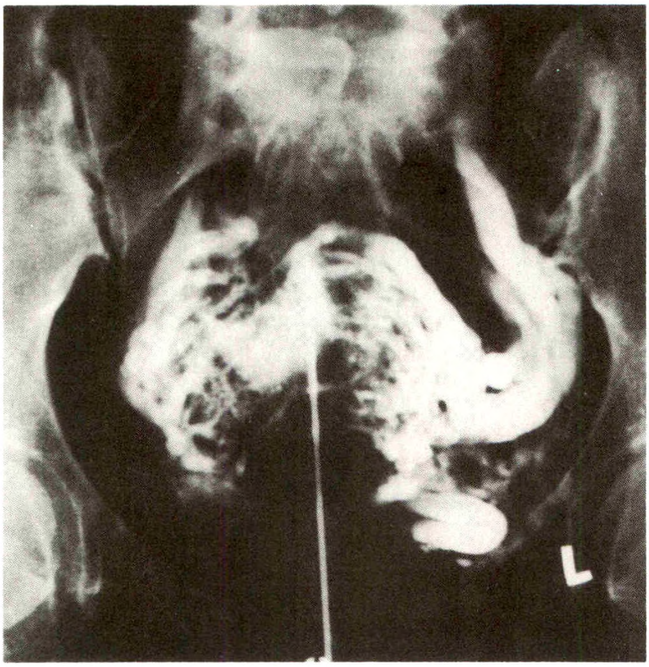

Fig. 1. Abnormal pelvic venogram taken at the end of injection of contrast medium. Note the dilated ovarian veins. The right ovarian vein is seen crossing the transverse processes of the lower lumbar vertebrae. Congestion of the ovarian hilum is shown by the loss of definition of individual veins. Large dilated veins draining the myometrium can also be seen.

Patients and methods

A structured questionnaire was administered to, and a clinical examination performed by one of the two authors (P.W.R. and R.W.B.) on 68 consecutive patients with a history of chronic lower abdominal pain seen in the Pelvic Pain Clinic at the Samaritan Hospital for Women. On laparoscopy, 25 women had evidence of pelvic pathology and 43 did not. Of these 43 women, 35 (group 1) had evidence of pelvic congestion on pelvic venography (Fig. 1). Eight were excluded either because they had a normal venogram or venography had not been done. Of the 25 women with pelvic pathology, 22 (group 2) had no evidence of pelvic congestion on venography (Fig. 2). Specific pathology in this group was endometriosis in 10 women, obvious old pelvic inflammatory disease in 11 and one had fibroids. The questionnaire was also administered to, and a clinical examination performed on 36 women admitted for sterilization during this period (group 3). None of them complained of pelvic pain and pelvic venography was not done. At laparoscopy all but one were found to have normal pelvic organs.

The characteristics of the women in each group are compared in Table 1. Only 29% were nulliparous in group 1 compared with 77% in group 2, while all the women in group 3 were parous. The three groups are similar in age, ethnic origin and educational status. The possibility of diagnostic overlap between groups 1 and 2 was raised by us in a previous study (Beard *et al.* 1977) but has been minimized in this study by pelvic venography.

Statistical analyses

All categorical data were analysed by either the χ^2 test modified by the Yates' correction or Fisher's exact test when the expected number in any cell was less than 5. When the two groups of pelvic pain patients were compared with group 3, the χ^2 was partitioned to allow comparison of groups 1 and 2. Data for duration of pain in Table 1 were not normally distributed so the Mann–Whitney *U*-test was used to test the significance of the difference between the groups.

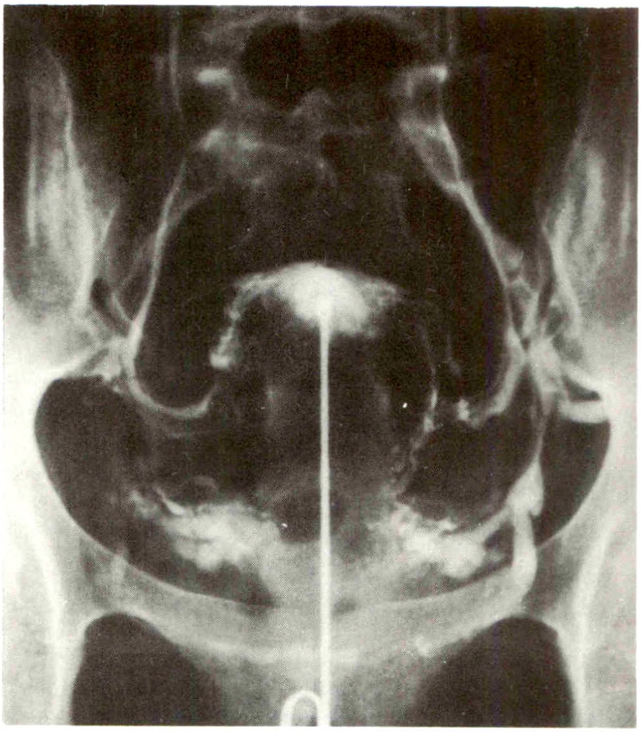

Fig. 2. Normal pelvic venogram taken at the end of injection of contrast medium. Note the virtual disappearance of dye which has already drained into the circulation. Narrow ovarian veins are shown bilaterally with the outline of the ovarian hilum. Five veins draining the myometrium can just be discerned.

Table 1. Characteristics of the patients and their pain

	Group 1 ($n = 35$)		Group 2 ($n = 22$)		Group 3 ($n = 36$)	
Mean age (years)	32·4		29·5		34·6	
Range	21–41		18–41		26–42	
Nulliparous	10	(29%)	17	(77%)	0	
Multiparous	25	(71%)	5	(23%)	36	(100%)
Single/divorced	12	(34%)	15	(68%)	9	(25%)
Married	23	(66%)	7	(32%)	27	(75%)
Duration of pain (months)						
Median	30		24			
Range	6–240		6–108		$P<0{\cdot}25$	
Nature						
Dull ache	11		10		$P<0{\cdot}5$	
Dull and sharp	15		3			
Other types	9		9			
Acute/severe episodes	33		9		$P<0{\cdot}001$	
Position						
Right iliac fossa	14		5		$P<0{\cdot}05$	
Left iliac fossa	7		2			
Both	12		4			
Other	2		11			
Pain moves	23		5		$P<0{\cdot}01$	

Definitions

Pelvic congestion. This was diagnosed at pelvic venography by the presence of ovarian vein dilatation, stasis (as evidenced by slow clearance of dye) and visual evidence of vascular congestion in the ovarian plexus. These are assessed objectively by a scoring system (Beard *et al.* 1984). A score of ≥5 is abnormal and indicates the presence of this condition.

Chronic pelvic pain. A history of lower abdominal pain for ≥6 months.

Pelvic inflammatory disease. The finding at laparoscopy of adhesions in the pelvis.

Dysfunctional menstrual bleeding. Defined as heavy bleeding (clots), or prolonged bleeding (>7 days) or irregular bleeding with a cycle varying more than 6 days.

Dysmenorrhoea, 'congestive'. Pain starting before the onset of menstruation.

Dysmenorrhoea, 'spasmodic'. Pain starting on or after the first day of menstruation.

Regular sexual intercourse. A stated frequency of intercourse of at least once a week.

Postcoital ache. A persistent pain starting after intercourse and lasting for a variable time up to 24 h.

The 'ovarian point'. An anatomical landmark situated at the junction of the upper and middle thirds of a line drawn between the umbilicus and the anterior superior iliac spine.

Congested cervix. Blueing of the cervix, often spreading to the vagina, similar to that seen in pregnancy.

Results

Duration, nature and position of the pain (Table 1)

The median duration of the pain was not significantly longer in group 1 than in group 2 (30 compared with 24 months). In both groups the nature of the pain was dull with occasional sharp episodes. There were, however, more acute severe episodes of pain in group 1 sufficient to result occasionally in emergency admission to hospital.

The side of the abdomen on which the pain commonly occurred was not a useful distinguishing feature between groups. However, the women in group 1 more often admitted that the same pain was sometimes felt on the opposite side to the side complained of. In group 2 the position of the pain was more often constant.

Factors exacerbating and alleviating the pain (Table 2)

Factors such as walking, standing, lifting and bending which tended to exacerbate the pain more often in group 1 than 2. Stress (tension or excitement) was more often mentioned as exacerbating the pain by women in group 1. Various factors which alleviated the pain were mentioned by 71% in group 1 and by 50% in group 2 while overall there was no significant difference between the groups. Lying down and analgesics tended to be more helpful for the women in group 1.

Associated symptoms (Table 3)

Associated symptoms, in particular backache, vaginal discharge and headache occurred significantly more frequently in group 1.

Surgical and medical history (Table 4)

Groups 1 and 2 were compared with the control group 3 to determine the frequency of medical and surgical conditions commonly reported by women with pelvic pain.

Sixteen women (46%) in group 1 and nine (41%) in group 2 had been told at some time before coming to the clinic that they were suffering from pelvic inflammatory disease compared with 8% in group 3. Nine women in group 2 had suspected pelvic inflammatory disease, in all of whom it was confirmed at laparoscopy while in group 1 it was suspected in 16 (46%) and proven in none. Appendicectomy was performed more commonly in women complaining of pain from whatever cause, tending to be more frequently done in women with pelvic congestion (group 1). The prevalence of varicose veins in the legs was similar in all three groups.

Menstrual and sexual history (Table 5)

Dysfunctional bleeding was significantly more frequent in group 1 (54%) than in groups 2 and 3 (27% and 22%). Dysmenorrhoea was more common in groups 1 and 2 than in group 3 but in group 1 the dysmenorrhoea was 'congestive' (89%) whereas in groups 2 and 3 it was more only 'spasmodic' (81% and 72% respectively). Regular sexual intercourse was less common

Table 2. Factors which exacerbate and alleviate the pain

Factors	Group 1 ($n = 35$)	Group 2 ($n = 22$)	
Exacerbating factors present	30 (86%)	11 (50%)	$P<0{\cdot}01$
Walking	17	4	
Standing	14	4	
Lifting	17	1	
Bending	7	1	
Stress	8	1	
Alleviating factors present	25 (71%)	11 (50%)	$P<0{\cdot}25$
Lying down	18	5	
Analgesics	18	4	
Local heat	9	2	
Relaxation	9	2	
Antibiotics	0	1	

Table 3. Major associated symptoms

Symptoms	Group 1 ($n = 35$)	Group 2 ($n = 22$)	
Number with one or more additional symptoms	33	15	$P<0{\cdot}05$
Backache	21 (60%)	7 (32%)	
Vaginal discharge	16 (46%)	5 (23%)	
Headache	19 (54%)	6 (27%)	

Table 4. Surgical and medical history

History	Group 1 ($n = 35$)	Group 2 ($n = 22$)	Group 3 ($n = 36$)
Pelvic inflammation			
Suspected	16 (46%)	9 (41%)	3 (8%)
Proven	0	11	1
Endometriosis	0	10	0
Appendicectomy	12 (33%)•	4 (18%)	4 (11%)°
Other abdominal surgery (excluding laparoscopy)	6•	5	6•

χ^2 for all three groups: •$P>0{\cdot}05$; χ^2 partitioned for groups 1 and 2: •$P>0{\cdot}05$.

amongst women in group 1 compared with those in group 2. Deep dyspareunia was a common symptom in both the pain groups (71% and 41%) compared with group 3 (11%) and occurred significantly more frequently in group 1 than 2. Postcoital ache was found in 65% in group 1 compared with 9% in group 2 and 8% in group 3.

Frequency of factors likely to be associated with emotional disturbance (Table 6)

Chronic emotional disturbance has been reported in women with no obvious pathology to account for their pain (Beard *et al.* 1977; Duncan & Taylor 1952). In this study, we have compared the frequency of occurrence of the following factors likely to be a precipitating cause or a part of chronic emotional disturbance.

Factors in childhood: (i) death of one or both parents, (ii) parents divorced or separated, (iii) brought up by one or neither parent, (iv) unhappy memories of childhood. Factors in present life: (i) divorced, separated or unhappy with husband, for married women, (ii) current

Table 5. Menstrual and sexual history

History	Group 1 ($n = 35$)	Group 2 ($n = 22$)	Group 3 ($n = 36$)
Dysfunctional bleeding	19 (54%)‡	6 (27%)	8 (22%)*
Dysmenorrhoea	27 (77%)•	16 (73%)	18 (50%)*
Spasmodic	3	13	13
Congestive	24	3	5
Regular sexual intercourse	19 (54%)‡	16 (73%)	30 (83%)**
Dyspareunia	25 (71%)‡	9 (41%)	4 (11%)***
Postcoital ache	23 (65%)‡‡‡	2 (9%)	3 (8%)***

χ^2 for all three groups: **P*<0·05, ***P*<0·01, ****P*<0·001. χ^2 partitioned for groups 1 and 2: •*P*>0·05, ‡*P*<0·05, ‡‡‡*P*<0·001.

Table 6. Factors associated with emotional disturbance

	Group 1 ($n = 35$)	Group 2 ($n = 22$)	Group 3 ($n = 36$)
One or more emotional factors	21 (60%)•	8 (36%)	10 (27%)*

χ^2 for all three groups: **P*<0·05. χ^2 partitioned for groups 1 and 2: •*P*>0·05.

Table 7. Physical signs on vaginal examination

Physical signs	Group 1 ($n = 35$)	Group 2 ($n = 22$)	Group 3 ($n = 36$)
Ovarian point tenderness	22 (77%)‡‡‡	4 (18%)	5 (15%)***
Cervix			
Congested appearance	6 (17%)•	3 (14%)	2 (6%)•
Excitatation pain/upward movement	16 (46%)‡‡‡	1 (5%)	2 (6%)***
Uterus			
Anteverted/vertical	23 (66%)•	18 (82%)	24 (67%)•
Bulky	14 (40%)•	8 (36%)	15 (42%)•
Tender on pressure	20 (57%)•	9 (41%)	2 (6%)***
Ovaries			
Tender	30 (86%)‡‡‡	7 (32%)	9 (25%)***
Enlarged	6 (17%)•	1 (5%)	3 (8%)•

χ^2 for all three groups: •*P*>0·05, ****P*<0·001 χ^2 partitioned for groups 1 and 2: •*P*>0·05, ‡‡‡*P*<0·001.

or recent close relationship unhappy, for single women.

Table 6 shows that there is a tendency for women in groups 1 and 2 to have more emotional disturbance than those in group 3. There was no significant difference in the frequency between groups 1 and 2.

Abdominal examination (Table 7)

The finding of ovarian point tenderness on deep palpation was a more common sign in group 1 (77%) than in groups 2 (18%) and 3 (14%).

Vaginal examination (Table 7)

The cervix appeared congested in a few women in all groups and this was not a distinguishing physical sign between groups. Lateral or upward movement of the cervix elicited excitation pain significantly more often in group 1 (46%) than in groups 2 (5%) and 3 (6%) respectively. The position of the uterus, its size and tenderness of the uterosacral ligaments did not prove to be useful distinguishing features between groups. Tenderness during bimanual compression of the uterus was significantly more frequent in groups 1 and 2

(57% and 41%) than in group 3 (6%). The most useful distinguishing physical sign proved to be the marked ovarian tenderness elicited by gentle compression on vaginal examination. In 86% of women in group 1, one or both ovaries were tender compared with 32% in group 2 and 25% in group 3. This difference is highly significant.

Combination of symptoms

Marked differences were observed between groups 1 and 2 for many of the reported symptoms or clinical findings. The symptoms and findings were combined in a variety of ways to try to discriminate between women with pelvic congestion and those with other specific pelvic pathology. The most discriminating combination of symptoms and signs was postcoital ache and ovarian point tenderness. If either or both of these symptoms were present, the discrimination between groups 1 and 2 was 94% sensitive and 77% specific. Other combinations which also discriminated well were postcoital ache and/or ovarian tenderness (97% sensitive, 64% specific) and also ovarian point tenderness and/or pain reported as moving from one side to the other (94% sensitive and 68% specific).

Discussion

The study has shown that careful questioning and examination of women presenting with pelvic pain of more than 6 months duration can, with some certainty, distinguish those with pelvic congestion from those with some other cause for their pain.

We have observed that a history of postcoital ache and/or ovarian point tenderness provides the best discrimination between the two groups of women, and it would be valuable to see whether this was observed in a larger series or whether this was specific to these study groups.

One of the most striking features of pelvic congestion is that the condition is confined to women of reproductive age. Steege (1983), reviewing five studies of women with pelvic pain syndrome, noted that the mean age ranged from 28 to 34 years. In our study the mean age was 32·4 with a range of 21–41 years. We concur with Taylor (1954) who noted in his study of 205 women that 'no instance of this condition occurring after the menopause is reported in this series'. This is an important observation for not only is it of diagnostic value but it also provides a clue to the aetiology of the condition.

Typically, the pain of pelvic congestion is a dull ache similar in character to that in the legs complained of by individuals with varicose veins. Commonly, the pain is present only on one side, but direct questioning usually reveals that in most women it occasionally occurs on the other side. This is an important distinguishing feature from the pain of, for example, endometriosis which tends to be constant in position. The pain of pelvic congestion is brought on by walking or exacerbated by movement such as using a vacuum cleaner or a sudden rise in intra-abdominal pressure from lifting an object.

Over the years, pelvic congestion has been the most popular explanation for the pain (Renaer *et al.* 1980). The dull aching, the congestive dysmenorrhoea, the postcoital ache and the close association with dilated pelvic veins support this concept. It also seems likely that the numerous additional complaints of these patients such as backache, excessive vaginal discharge, deep dyspareunia and urinary symptoms (Taylor 1954), often cited as evidence of the neuroticism of these women are, in reality, due to the general pelvic congestion. Corroborative evidence that dilation and congestion in the pelvic veins is a cause of the pain has recently been produced from our group by performing pelvic venograms on women with pelvic pain syndrome during an acute attack of pain. When a selective venoconstrictor, dihydroergotamine, was administered intravenously during an acute attack of pain, a narrowing of the dilated veins with reduction of the congestion and diminution in pain was observed (Reginald *et al.* 1987).

The findings on vaginal examination reported in our study are to some extent at variance with those of other authors. We have found that the most diagnostically useful sign of pelvic congestion is tenderness of one or both ovaries. This observation was supported by the finding of abdominal tenderness over the ovarian point which we have shown as probably being due to compression of the ovarian vein with resultant back-pressure on the hilum of the ovary (Beard *et al.* 1984). We also found that the pain elicited when one or both ovaries are gently compressed during a vaginal examination is the same as the pain complained of, and is the most common physical sign in pelvic congestion, 86% in our series compared with 27% in the series reported by Taylor (1954). In contrast to our findings, both Renaer (1981) and Taylor (1949*b*) stress that tenderness of the posterior parametrium and uterosacral ligaments is the most useful diagnostic sign (present in more than 80% of their patients). We too observed that upward movement of the cervix produced pain but only in 46% of our patients in group 1 and the discrepancy between the studies may be due to when and how the vaginal examination is performed. When a patient says she is free of pain, tenderness can nearly always be elicited by gentle ovarian compression, whereas much more vigorous manipulation of the cervix and uterosacral ligaments is required to elicit tenderness. Again, in contrast to Renaer (1981), we found the uterus to be tender in 57% of the women in group 1.

Truc & Musset (1973), reviewing the literature, found a close association between pelvic pain, retroversion of the uterus and dilated pelvic veins. Allen & Masters (1955) have made much of this association ascribing the condition to laceration of the broad ligament. Our experience, like that of Taylor (1949*b*), has been different. In our study, the position of the uterus was the same in patients with pelvic congestion as in those in the control group. Like Renaer (1981), we rarely found a 'laceration' of the broad ligament as described by Allen & Masters (1955). More often it has proved to be a chance finding in women being investigated for conditions other than pelvic pain.

Taylor (1949*b*) reported that in only 15% of his patients was the uterus bulky and the ovaries enlarged. In contrast, we found that the uterus was enlarged in 40% but this was not different from our control series. The disparity in findings is almost certainly due to the unreliability of clinical assessment of uterine size, particularly when the enlargement is not marked. Our current studies using ultrasound scanning which is a more reliable method show that the size of the uterus is increased.

One of the more striking features of the history of the women with pelvic congestion is the frequency with which pelvic inflammatory disease has been diagnosed in the past, usually for no other reason than the supposition that young women are more likely to have a sexually transmitted disease. Once such a diagnosis is made, usually without laparoscopic evidence, each subsequent attack of pain is regarded by the patient's doctor as a recurrence of inflammation and is treated with antibiotics. Inevitably, such a sequence of events reinforces the fear of young women, looking forward to having children some day, that they have tubal pathology which will make them infertile. This repetitive sequence of symptoms/diagnosis/treatment creates what has been described as the 'pelvic cripple' (Leading Article 1981). In our study, 46% of the women with pelvic congestion believed they had recurrent pelvic inflammatory disease. Likewise, there is also a tendency to resort to abdominal surgery for supposed pelvic pathology in these women. Taylor (1954) reported in his series of 205 women that 90 had had abdominal operations ranging from appendicectomy to ovarian and uterine surgery. The high rate of gynaecological surgery in relatively young women cannot be justified. There is too much of a tendency for surgeons to assume that any unusual finding in the pelvis is a cause of the pelvic pain complained of (Kresh *et al.* 1984). We have found that 56% of women with pelvic congestion have polycystic ovaries (J. Adams *et al.*, unpublished observations) and quite commonly follicular cysts are present. These single cysts are transitory and cannot be the cause of the chronic pain, but they are often removed, leading to tubo-ovarian adhesions which may impair fertility. Our study also shows that a history of appendicectomy is common amongst women with pelvic congestion, which suggests that many of them had a normal appendix removed when no other cause for the pain could be found.

Emotional disturbance amounting to psychological illness has been frequently reported for women with chronic lower abdominal pain in the absence of pathology (Beard *et al.* 1977; Gidro-Frank *et al.* 1960; Benson *et al.* 1959). Duncan & Taylor (1952) studying 36 women with pelvic pain syndrome found that 'they had experienced in childhood almost no secure family life after which to pattern their own subsequent existence'. They went on to comment that in 34 women, the onset of the pain could be related to a stressful life situation. A previous study confirmed the tendency to diminished libido amongst women with pelvic congestion (Beard *et al.* 1977). In the present study, five factors were considered as indices of emotional disturbance and 60% of those with pelvic congestion had one or more such factors compared with a significantly lower rate of 27% in the group of normal women. This result is supported by the observation of Duncan & Taylor (1952) who noted that 29 of the 36 women with unexplained pelvic pain had had an unfavourable family environment in childhood which, they suggested, led to emotional disturbance in later life.

Laparoscopy remains an essential part of the investigation of pelvic pain because it is still the only reliable means of excluding endometriosis. In addition, we have found that careful inspection of the broad ligament and the hilum of the ovary reveals dilated veins that are usually regarded as being of no significance (Beard *et al.* 1986). We have also shown that polycystic ovaries, diagnosed by ultrasound, are usually visible through the laparoscope. Pelvic venography has proved to be an invaluable research tool. The procedure can be done on outpatients and has the great advantage that women can see the dilated veins on the television monitor. Although venography is an invasive procedure it is likely to remain a valuable investigation of pelvic pain because the congestion and vascular stasis are so well demonstrated. Ultrasound scanning is complementary to venography, being valuable for demonstrating dilated veins, polycystic ovaries and uterine enlargement (J. Adams *et al.*, unpublished observations).

The high prevalence of unexplained pelvic pain amongst young women is a cause of concern to hospital and general practitioners because it has been so difficult to do anything to relieve the pain. Because the pathophysiology was not understood many of these women were labelled as neurotic and having 'psychogenic' pain. At present various methods of treatment are being assessed by our group, but until the results of our current randomized controlled trial are available no definite recommendations can be made. In the interim it is hoped that practitioners will find it helpful to make a plausible diagnosis of this hitherto enigmatic condition.

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References

Allen, W. M. & Masters, W. H. (1955) Traumatic laceration of uterine support. *Am J Obstet Gynecol* **70,** 500-513.

Beard, R. W., Belsey, E. M , Lieberman, B A & Wilkinson, J C M (1977) Pelvic pain in women. *Am J Obstet Gynecol* **128,** 566-570.

Beard, R W., Highman, J H., Pearce, S. & Reginald, P. W. (1984) Diagnosis of pelvic varicosities in women with chronic pelvic pain *Lancet* **ii,** 946-949.

Beard, R W., Reginald, P W. & Pearce, S. (1986) Pelvic pain in women *Br Med J* **293,** 1160-1162

Benson, R. C., Hanson, K H. & Mattarazo, J (1959) Atypical pelvic pain in women; gynaecologic psychiatric considerations. *Am J Obstet Gynecol* **77,** 806-823

Duncan, C H. & Taylor, H. C (1952) A psychosomatic study of pelvic congestion. *Am J Obstet Gynecol* **64,** 1-12.

Gidro-Frank, L., Gordon, T & Taylor, H. C (1960) Pelvic pain and female identity *Am J Obstet Gynecol,* **79,** 1184-1202.

Kresh, A J., Seifer, D. B., Sachs, L. B. & Barresse, I. (1984) Laparoscopy in 100 women with chronic pelvic pain. *Obstet Gynecol* **64,** 672-674.

Leading Article (1981) Pelvic pain. *Lancet* **ii,** 617-618

Reginald, P. W., Beard, R W , Kooner, J. S , Mathias, C. J , Samarage, S V , Sutherland, I. A. & Wadsworth, J. (1987) Intravenous dihydroergotamine to relieve pelvic congestion with pain in young women *Lancet* **ii,** 351-353.

Renaer, M (1981) Chronic pelvic pain without obvious pathology. In *Chronic Pelvic Pain in Women.* Springer-Verlag, New York, pp. 162-175.

Renaer, M , Nijs, P., van Assche, A. & Vertommen, H (1980) Chronic pelvic pain without obvious pathology. Personal observations and a review of the problem. *Eur J Obstet Gynaecol Reprod Biol* **10,** 415-463.

Steege, J. F. (1983) Chronic pelvic pain: clinical perspectives. In *Handbook of Psychosomatic Obstetrics and Gynaecology* (Dinnerstein & Burrows, eds), Elsevier Biomedical Press, Amsterdam, pp. 401-412

Taylor, H C. (1949*a*) Vascular congestion and hyperaemia I. Physiological basis and history of the concept. *Am J Obstet Gynecol* **57,** 211-230

Taylor, H. C. (1949*b*) Vascular congestion and hyperaemia. II. The clinical aspect of congestion fibrosis syndrome *Am J Obstet Gynecol* **57,** 637-653

Taylor, H. C. (1949*c*) Vascular congestion and hyperaemia III Etiology and therapy. *Am J Obstet Gynecol* **57,** 654-668

Taylor, H. C. (1954) Pelvic pain based on a vascular and autonomic nervous system disorder. *Am J Obstet Gynecol* **57,** 1177-1196

Truc, J. B & Musset, R (1973) Pathologie du tissu cellulaire pelvien et grossesse. In *Le Tissu Cellulaire Pelvien* (De Brux, J., ed.), Masson, Paris.

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Increased uterine prostaglandin E receptors in menorrhagic women

JUAN MARIA ADELANTADO, MARGARET C. P. REES, ANDRÉS LÓPEZ BERNAL, ALEXANDER C. TURNBULL

Summary. PGE receptor concentrations were measured in myometrial samples collected from 10 women at hysterectomy. Five women had normal measured menstrual blood loss (35–44 ml) and the remainder had unexplained menorrhagia occurring in the absence of any uterine, pelvic or general pathology, with losses ranging from 85 to 925 ml. Median PGE receptor concentrations were significantly higher in the women with menorrhagia (1077 fmol/mg protein) than in the women with normal menstrual blood loss (625 fmol/mg protein) and correlated with menstrual blood loss ($P<0{\cdot}02$). These findings suggest that unexplained menorrhagia may simply be a constitutional variant in some women and that specific and potent PGE uterine receptor antagonists would furnish effective non-surgical treatment for unexplained menorrhagia.

Unexplained menorrhagia, occurring in the absence of uterine, pelvic or general pathology, is a common clinical problem, associated with excessive uterine prostaglandin (PG) levels. PG synthetase inhibitors can reduce menstrual blood loss in this condition and have been used successfully in its treatment (Willman *et al.* 1976; Anderson *et al.* 1976; Fraser *et al.* 1983). However, when PG levels in endometrium, myometrium and menstrual fluid have been related to total menstrual blood loss, results have been conflicting (Smith *et al.* 1981; Rees *et al.* 1984*a*, *b*). We have therefore investigated the potential role of PG receptors in the uterus in unexplained menorrhagia. PGs are thought to act through receptors in the cell membrane. PG receptors have been detected in human myometrium but not endometrium (Wakeling & Wyngarden 1974; Carsten & Miller 1981; Bauknecht *et al.* 1981), and are occupied by PGs of the E series in preference to $PGF_2\alpha$ (Bauknecht *et al.* 1981; Hofman *et al.* 1983; Giannopoulos *et al.* 1985).

It has been reported that binding of PGE to myometrium was higher in women with unexplained menorrhagia than in those with dysmenorrhoea, but menstrual blood loss was not measured in that study (Hofman *et al.* 1983). Such measurements are essential because there is such a poor relation between subjective and objective assessments of menstrual bleeding (Chimbira *et al.* 1980; Fraser *et al.* 1984). In one study, less than 40% of women complaining of menorrhagia actually had menstrual losses >80 ml (Fraser *et al.* 1984). In this study, we have estimated PGE receptors in myometrial samples in women with pain-free periods with menstrual losses which had been found by direct measurement to be normal (<80 ml) or excessive (>80 ml) (Hallberg *et al.* 1966).

Patients and methods

Myometrial samples were obtained from 10 women at hysterectomy. Operations were indi-

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Nuffield Department of Obstetrics and Gynaecology, University of Oxford, John Radcliffe Hospital, Headington, Oxford OX3 9DU
JUAN MARIA ADELANTADO *Research Fellow*
MARGARET C. P. REES *Research Fellow*
ANDRÉS LÓPEZ BERNAL *Research Fellow*
ALEXANDER C. TURNBULL *Professor*

Correspondence. Margaret C. P. Rees

cated because of a complaint of menorrhagia in the absence of pelvic pathology. The women were aged between 35 and 45 years and had regular (26–33 days) menstrual cycles. None had used either oral or intrauterine contraception or received any hormone therapy for at least 6 months before surgery. None had been treated with PG synthetase inhibitors in the cycle preceding hysterectomy. Menstrual blood loss, which had been estimated by the alkaline haematin method (Hallberg & Nilsson 1964) for two periods before operation, ranged from 35 to 925 ml, with five women having menorrhagia (>80 ml) (Hallberg *et al.* 1966). Specimens from the uterine corpus were obtained throughout the menstrual cycle but not during menstruation (see below). Permission was obtained from the Oxford Ethics Committee.

Estimation of prostaglandin E receptors

The uterus was opened immediately after removal and a portion of myometrium, freed from endometrial and peritoneal layers, was washed in 0·15 M NaCl, frozen in solid CO_2 and stored at −70 °C. Under these conditions the samples were stable for at least 2 weeks. The concentration (fmol/mg protein), and affinity (Kd, nM) of PGE receptors were measured as described previously (Adelantado *et al.* 1985; Adelantado 1985). The samples were incubated with varying concentrations (0·25–25 nM) of radiolabelled PGE_2 with and without a 1000-fold excess of non-labelled PGE_2. Optimal binding was achieved after 45 min at 20 °C. Non-specific binding averaged 10% of total binding. Nonparametric tests (Mann-Whitney and Spearman rank correlations) were employed since menstrual blood loss is not normally distributed.

Preliminary validation studies showed no statistically significant differences in ^3H-PGE_2 binding at different phases of the menstrual cycle. The median and range of receptor concentrations in the follicular phase were 720 (369–983) fmol/mg protein, with a Kd of 1·5 (1·1–1·9 nM; $n = 5$) and corresponding values in the luteal phase were 834 (256–1161) fmol/mg protein with a Kd of 1·7 (1·0–2·3; $n = 15$).

Results

Table 1 shows that the concentration of PGE receptors was significantly higher in women with excessive menstrual blood loss (>80 ml) than in those with normal blood loss (Hallberg *et al.* (1966): 1077 (730–1400) (median and range) compared with 625 (175–758) fmol/mg protein ($P<0·02$). The calculated affinity of the receptors (Kd) in the two groups was similar. There was a significant positive relation between menstrual blood loss and myometrial PGE receptor concentrations across the whole range (r_s 0·639, $P<0·05$).

Discussion

The presence of PGE binding sites in human myometrium has been confirmed (Wakeling & Wyngarden 1974; Carsten & Miller 1981; Bauknecht *et al.* 1981). Their high affinity and specificity accords with their being true PG receptors and the myometrial PGE receptor concentrations and their apparent Kd are similar to values reported by other authors (Bauknecht *et al.* 1981; Giannopoulos *et al.* 1985). Hofman *et al.* (1983) reported lower concentrations but this discrepancy could be explained by the different temperature of incubation and technique to separate free and bound ligand.

This is the first report of a significant direct correlation between myometrial PGE receptor concentration and measured menstrual blood loss. Higher concentrations were found in women with unexplained menorrhagia than in women with normal menstrual loss, confirming a previous report (Hofman *et al.* 1983) that myometrial PGE receptors could be increased in women complaining of menorrhagia, although menstrual blood loss was not measured in that study

Table 1. ^3H-prostaglandin E_2 binding in human myometrium in relation to menstrual blood loss

Blood loss (ml)	Receptor concentration (fmol/mg protein)	Kd (nM)
35	620	1·5
35	758	1·0
37	697	1·1
40	175	1·1
44	625	2·2
85	1077	1·5
112	1208	1·1
137	1024	1·2
197	730	1·1
925	1400	2·4

PGE is a vasodilator and could potentially affect menstrual blood loss (Moncada & Vane 1979), but our current techniques cannot distinguish between myometrial and vascular binding sites and further work is required. The tendency to greater PGE production described in the endometrium of menorrhagic women (Smith *et al.* 1981) suggests an altered response to this PG which could be accounted for by increased PGE receptor levels. Furthermore, our data provide another pointer to the mode of action of fenamates used to reduce menstrual blood loss. These agents not only reduce PG synthesis but also act at the receptor level (Sanger & Bennett 1979; McClean & Gluckman 1983) possibly by interfering with PGE binding, a topic currently under investigation in this laboratory.

Our findings also suggest that unexplained menorrhagia may simply represent a constitutional variation in some women in accord with the study by Hallberg *et al.* (1966) who found no significant change with age in the distribution of menstrual blood loss. If increased myometrial PGE receptor concentrations are causally related to unexplained menorrhagia, potent and specific antagonists of uterine PGE receptors should provide effective medical treatment for this common disorder.

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References

Adelantado, J. M (1985) Hormonal studies in reproductive tissues a receptor approach *MSc Thesis*, University of Oxford

Adelantado, J. M., Humphries, J., Lopez Bernal, A & Turnbull, A C. (1985) Is there a topographical distribution of prostaglandin E_2 receptors in the human pregnant uterus? In *The Physiological Development of the Fetus and Newborn* (Jones, C. T. & Nathanielsz, P W., eds), London Academic Press, pp 489-492

Anderson, A B M., Haynes, P J , Guillebaud, J & Turnbull, A C. (1976) Reduction of menstrual blood loss by prostaglandin synthetase inhibition. *Lancet* **i**, 774-776

Bauknecht, T., Krahe, B., Rechenbach, U., Zahradnik, H P & Breckwoldt, M. (1981) Distribution of prostaglandin E_2 and prostaglandin $F_2\alpha$ receptors in human myometrium *Acta Endocrinol* **98**, 446-450

Carsten, M E & Miller, J. D (1981) Prostaglandin E_2 receptor in the myometrium: distribution in subcellular fractions *Arch Biochem Biophys* **212**, 700-704

Chimbira, T. H , Anderson, A. B. M. & Turnbull, A C (1980) Relation between measured menstrual loss and the patient's subjective assessment of loss, duration of bleeding, number of sanitary towels used, uterine weight and endometrial surface area. *Br J Obstet Gynaecol* **87**, 603-608

Fraser, I. S , McCarron, G., Markham, R., Robinson, M & Smyth, E (1983) Long term treatment of menorrhagia with mefenamic acid *Obstet Gynecol* **61**, 109-114

Fraser, I. S., McCarron, G & Markham, R (1984) A preliminary study of factors influencing perception of menstrual blood loss volume *Am J Obstet Gynecol* **149**, 788-793.

Giannopoulos, G , Jackson, K , Kredentser, J. & Tulchinsky, D. (1985) Prostaglandin E and $F_2\alpha$ receptors in human myometrium during the menstrual cycle and in pregnancy and labor *Am J Obstet Gynecol* **153**, 904-910.

Hallberg, L & Nilsson, L (1964) Determination of menstrual blood loss. *Scand J Clin Lab Invest* **16**, 244-248.

Hallberg, L , Hogdahl, A., Nilsson, L & Rybo, G. (1966) Menstrual blood loss—a population study *Acta Obstet Gynecol Scand* **45**, 320-351.

Hofman, G. E , Rao, C. V , Barrows, G. H. & Sanfilippo, J S (1983) Topography of human uterine prostaglandin E and $F_2\alpha$ receptors and their profiles during pathological states *J Clin Endocrinol Metab* **57**, 360-366.

McClean, J. R. & Gluckman, M. I. (1983) On the mechanism of the pharmacologic activity of meclofenamate sodium *Arzneimittelforschung* **33**, 627-632.

Moncada, S. & Vane, J R (1979) Pharmacology and endogenous roles of prostaglandin endo-peroxides, thromboxane A_2 and prostacyclin. *Pharmacol Rev* **30**, 293-332

Rees, M. C. P , Anderson, A. B M , Demers, L M & Turnbull, A. C (1984*a*) Prostaglandins in menstrual fluid in menorrhagia and dysmenorrhoea *Br J Obstet Gynaecol* **91**, 673-680.

Rees, M. C P , Anderson, A. B M., Demers, L. M. & Turnbull, A C. (1984*b*) Endometrial and myometrial prostaglandin release during the menstrual cycle in relation to menstrual blood loss. *J Clin Endocrinol Metab* **58**, 813-818.

Sanger, G. J. & Bennett, A (1979) Fenamates may antagonise the actions of prostaglandin endo-peroxides in human myometrium. *Br J Clin Pharmacol* **8,** 479-484.

Smith, S. K., Abel, M. H , Kelly, R W. & Baird, D. T. (1981) Prostaglandin synthesis in the endometrium of women with ovular dysfunctional uterine bleeding. *Br J Obstet Gynaecol* **88,** 434-442.

Wakeling, A E. & Wyngarden, L J. (1974) Prostaglandin receptors in the human, monkey and hamster uterus. *Endocrinology* **95,** 55-64.

Willman, E A., Collins, W P & Clayton, S. G. (1976) Studies on the involvement of prostaglandins in uterine symptomatology and pathology. *Br J Obstet Gynaecol* **83,** 337-341

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A randomized trial of progestogens in the primary treatment of endometrial carcinoma

R. R. MACDONALD, JANE THOROGOOD, M. K. MASON

Summary. A randomized trial was arranged in Yorkshire to assess whether progestogens would improve survival as part of the primary treatment of endometrial carcinoma, in conjunction with surgery and radiotherapy. A total of 429 patients was randomized on diagnosis to the progestogen or control group and treated locally according to an agreed protocol. All the patients are now more than 1 year after operation and over half are more than 5 years after operation. The projected overall 5-year survival rate is 76% but contrary to expectation there is no statistically significant difference in survival between the patients treated with progestogens and the control group even after statistical adjustment for known prognostic factors.

Five-year survival for patients with endometrial carcinoma remains disappointing with an overall crude survival rate in England and Wales of just 56·8%. The survival rate, allowing for deaths from other causes, is 66·1% in England and Wales and 66·5% in Yorkshire (Joslin & Thorogood 1986). The standard surgical treatment is total hysterectomy with bilateral salpingo-oophorectomy. Since the risk of lymph gland involvement varies with the stage and nature of the tumour, radical Wertheim's hysterectomy has been advocated for undifferentiated and invasive tumours (Lewis *et al.* 1970) but without evidence of improved survival after surgery. Postoperative intravaginal irradiation has reduced vaginal recurrence (Dobbie 1953) and there are claims that high energy radiation to the pelvic lymph glands reduces pelvic recurrence and improves survival (Joslin *et al.* 1977; Joslin 1986), but there remains a need for a fresh approach.

Prolonged unopposed oestrogen stimulation is believed to be a major factor in the aetiology of endometrial carcinoma (Braunstein 1984). In patients with recurrent endometrial carcinoma high-dose progestogen therapy induces objective remission in 30–40% (Taylor 1975) and progestogens have been recommended as part of the primary treatment (Taylor 1979). Apparent cure from endometrial carcinoma has been reported recently in younger patients treated with progestogens alone (Bokhman *et al.* 1985; Thornton *et al.* 1985). We felt that there was a case for a randomized controlled trial to decide whether progestogens, in association with surgery and radiotherapy, were of any value as part of the primary treatment of endometrial carcinoma.

Patients and methods

The drug chosen was medroxyprogesterone acetate (MPA) which can be given by intramuscular injection or by mouth as 100-mg tablets. As a group, the acetoxy progestogens are potent pro-

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Department of Obstetrics and Gynaecology, Clarendon Wing, The General Infirmary, Belmont Grove, Leeds LS2 9NS
R. R. MACDONALD *Consultant in Obstetrics and Gynaecology*

Yorkshire Regional Cancer Organization, Cookridge Hospital, Leeds LS16 6QB
JANE THOROGOOD *YRCO Data Processor*

Department of Pathology, St James's (University) Hospital, Beckett Street, Leeds
M. K. MASON *Consultant Pathologist*

Correspondence: R. R. Macdonald

gestational agents with minimal side-effects even at high dose rates. MPA has a weak corticosteroid effect at 300 mg per day but not at 100 mg per day (Macdonald 1973).

A working party composed of gynaecologists, radiotherapists and pathologists in the Yorkshire region agreed a protocol for standard treatment with surgery and radiotherapy which could be given locally throughout the region. It was postulated that the addition of progestogen therapy as part of the primary treatment would be likely to improve survival, especially in the patients with well-differentiated tumours. Ethical approval was sought in each district to allow random allocation so that approximately half the patients would have pre- and postoperative progestogen therapy in addition to the standard surgery and radiotherapy.

The only exclusions from the trial were patients with stage IV disease whose treatment would normally differ from the protocol, and any patient taking other hormone therapy at the time of diagnosis. In the event of drug side-effects the gynaecologist had the option to discontinue treatment but surveillance continued. It was agreed that if the tumour recurred, further treatment should be given at the discretion of the local gynaecologist, and the end point of the trial would be the death of the patient from tumour or other cause.

Dr Ian Sutherland kindly supplied prenumbered cards in sealed envelopes to allow random allocation by telephone from the regional oncology centre. He indicated that it would be necessary to aim at a total number of patients entering the trial which would be expected to yield eventually something like 60–70 deaths in order to exclude a mortality difference of 10%. In the event we calculated that with an expected survival in the control group of 75% we would need to observe 111 deaths in order to detect a 10% improvement in survival with 90% power and α of 5%.

When endometrial carcinoma was diagnosed on curettage the gynaecologist notified the regional oncology centre, and with informed consent the patient was randomly allocated to the control or progestogen group without any stratification by age or grade of tumour.

The treatment schedule included total hysterectomy with bilateral salpingo-oophorectomy for all patients followed by postoperative radiotherapy modified according to the site and extent of tumour. No radiotherapy was used in patients with well-differentiated tumours confined to the upper one third of the uterus with depth of invasion less than one third muscle thickness. Where the tumour involved the middle or lower one third of the uterus but not the endocervix, the patient was given intravaginal cathetron radiotherapy. Patients with more extensive tumour spread and all those with anaplastic tumours were treated with external radiation and cathetron radiotherapy to the upper third of the vagina.

Those patients randomized to the progestogen group received the following hormone therapy. As soon as possible after diagnostic curettage, and before hysterectomy, they were given intramuscular injections of 19 norhydroxyprogesterone caproate (gestronol, Depostat) in 100 mg daily for 5 days. Then from 7 days after hysterectomy they were treated with MPA (Provera) tablets, 100 mg three times a day for the first year and then 100 mg daily for at least 5 years. Clinical and pathological details were recorded on a special pathology form which was filed in the patient's notes. The diagnosis and grade of endometrial carcinoma were confirmed subsequently by a second, and if necessary, a third independent pathologist. The gynaecologists knew which patients were being given progestogens but the initial pathological assessment and subsequent review of the registration and follow-up forms was blind.

The trial began on 1 January, 1975 and registrations closed on 31 December, 1983. Each patient was reviewed at least every 6 months when a follow-up form was sent to the oncology centre. On death a postmortem was performed whenever the relatives agreed. Survival was calculated by the life-table method and compared between groups by the log rank test (Peto *et al.* 1977).

Initial assessment of the first 382 registrations showed no significant disparity between the groups, indicating that the drug therapy was not obviously harmful and so the trial was continued.

Five years after hysterectomy, additional information was requested about any change in blood pressure from registration, and about continuing coital function. Student's t-test was used to compare changes in blood pressure in each group.

Results

The total number of patients registered was 429, with 214 randomly allocated to the progestogen

Table 1. Reasons for withdrawal after overall analysis

Reasons	Progestogen group (*n* = 214)	Control group (*n* = 215)
Wrong diagnosis	16	24
Inoperable	15	15
Radiotherapy refused	3	6
No record forms	2	2
Total	36	47

group and 215 to the control group. The following details give results to the end of March 1985 when all the patients were more than 1 year after operation and over half the patients more than 5 years after operation.

The patients were entered in the trial on diagnosis after curettage. A number of patients were subsequently found to be inoperable, required more extensive surgery, declined radiotherapy or in the end had another diagnosis and those patients were classed as 'withdrawals' but were retained in the overall analysis to ensure an unbiased comparison of the two experimental groups; there were 36 withdrawals in the progestogen group and 47 in the control group (Table 1). At some stage a number of patientswere given different treatment from that intended, usually omission of the progestogen for more than a month but occasionally a control patient was given progestogen by mistake and those patients were classed as 'protocol deviations' (Table 2).

The total number of deaths to 31 March, 1985 was 116 (Table 3). Neither crude death rate nor analysis after removal of withdrawals shows any difference between the progestogen and control groups (Fig. 1) (log rank test, $P = 0{\cdot}62$ and $P = 0{\cdot}71$ respectively).

Table 4 shows the FIGO stages, degree of differentiation, depth of muscle invasion and age of the patients in the two treatment groups at entry, for all patients and after removal of the 'withdrawals'. The 95% confidence intervals for these factors are presented in Table 5.

It is of general interest that significant factors in survival were age ($P<0{\cdot}001$) (Fig. 2) with 100% survival under age 50, depth of muscle invasion ($P<0{\cdot}001$) (Fig. 3), FIGO stage (Fig. 4)

Table 2. Protocol deviations in patients included in the trial

Protocol deviation	Progestogen group (*n* = 214)	Control group (*n* = 215)
Incorrect drug treatment, iatrogenic error	13	7
Consultant chose treatment after randomization	4	6
Drug discontinued because of side-effects	23	–
Drug discontinued due to patient error	12	–
Total	52	13

Table 3. Assessment of deaths at 31 March, 1985

	Progestogen group (*n* = 214)	Control group (*n* = 215)
All patients		
Number alive	154	159
Number of deaths	60	56
Number of deaths in cases subsequently withdrawn from analysis		
Tumour deaths	12	13
Non-tumour deaths	9	8
Number of deaths in cases receiving incorrect treatment		
Tumour deaths	11	5
Non-tumour deaths	6	4
Number of deaths in full protocol group		
Tumour deaths	15	15
Non-tumour deaths	7	11

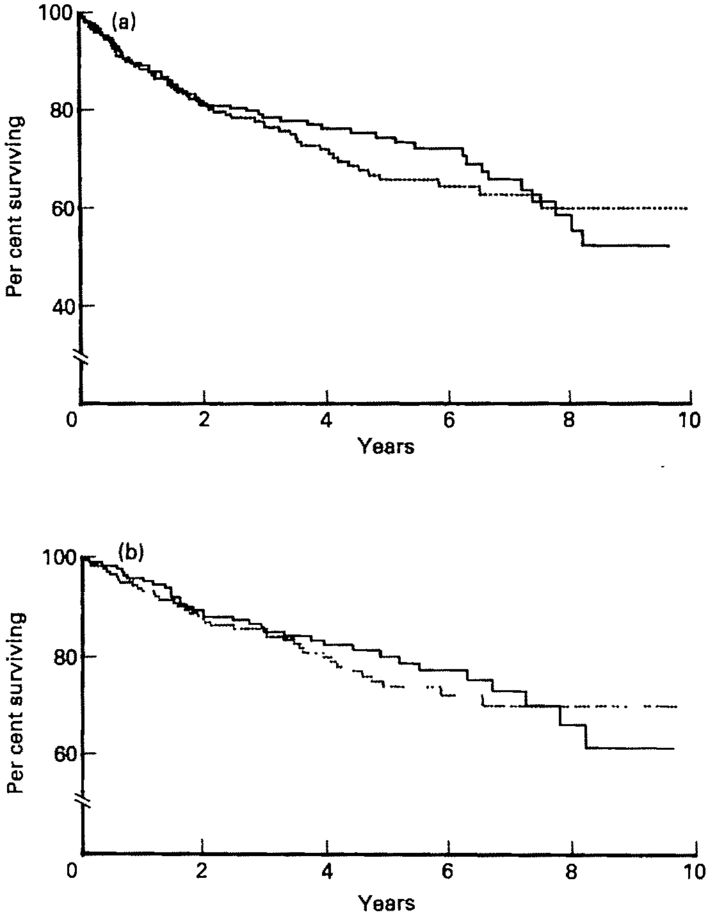

Fig. 1. Survival rate. (a) Overall: ——, Control (n = 215); . . , progestogen (n = 214); P = 0·6248. (b) After removal of withdrawals: ——, Control (n = 168); . ., progestogen (n = 178); P = 0·7116.

and differentiation (Fig. 5) but not progestogen treatment.

Side-effects associated with MPA therapy were few despite the initial high dose. Eight patients taking Provera were noted to have developed hypertension, and in one of them blood pressure returned to normal when the drug was discontinued but there was no overall difference in blood pressure between the two treatment groups at 5 years (systolic: t = 0·46, P>0·05; diastolic: t = 0·62, P>0·05). Cardiovascular deaths in the two groups are shown in Table 6.

Among 33 patients questioned about subsequent coital function, 10 out of 29 (5 in each group) who had been treated with postoperative intravaginal radiation had complete vaginal stenosis and were no longer coitally active.

On current data, after removal of withdrawals the probability of patients surviving 5 years is 73·4% in the progestogen group and 79·9% in the control group.

Discussion

At the start of the trial we had expected to find worthwhile additional benefit from treatment with progestogens with longer survival in the treated patients. In theory the 'operative umbrella' like an antibiotic might have prevented implantation of cancer cells disseminated at the time of hysterectomy, and improved the

Table 4. Distribution of patients by FIGO stage, differentiation, depth of muscle invasion and age at entry to the study

	All patients		Included patients only*	
Variable	Progestogen (n = 214)	Control (n = 215)	Progestogen (n = 178)	Control (n = 168)
FIGO stage				
IA	99	108	96	101
IB	47	47	45	43
II	26	13	24	11
III	19	16	13	13
IV	5	7	—	—
Differentiation				
Well	68	74	61	64
Moderate	75	74	68	65
Poor/anaplastic	54	46	48	39
Depth of invasion				
<½	85	88	79	80
≥½	94	94	86	80
Age group (years)				
<50	9	17	8	14
50–59	62	70	55	59
60–69	76	60	66	50
70+	67	68	49	45

* Excluding patients subsequently withdrawn (as detailed in Table 1) but including protocol deviations who received incorrect treatment.

Table 5. Prognostic factors and analysis of treatment effect allowing for these factors

	RR (95% CI)	*P*-value
(a) All patients		
Treatment group	1·09 (0·76 to 1·58)	0·63
FIGO stage	1·98 (1·69 to 2·31)	<0·0001
Differentiation	1·53 (1·19 to 1·96)	0·0007
Depth of invasion	2·44 (1·58 to 3·78)	<0·0001
Age group	2·22 (1·75 to 2·81)	<0·0001
Treatment group, allowing for:		
FIGO stage	0·99 (0·66 to 1·47)	0·95
Differentiation	1·06 (0·72 to 1·56)	0·76
Depth of invasion	1·17 (0·78 to 1·75)	0·45
Age group	1·04 (0·72 to 1·50)	0·83
(b) Included patients only*		
Treatment group	1·09 (0·69 to 1·72)	0·71
FIGO stage	1·65 (1·34 to 2·04)	<0·0001
Differentiation	1·42 (1·06 to 1·91)	0·02
Depth of invasion	2·30 (1·40 to 3·77)	0·0007
Age group	2·31 (1·72 to 3·10)	<0·0001
Treatment group, allowing for:		
FIGO stage	1·01 (0·63 to 1·60)	0·98
Differentiation	1·08 (0·69 to 1·71)	0·74
Depth of invasion	1·18 (0·74 to 1·87)	0·49
Age group	1·00 (0·63 to 1·58)	1·00

* See Table 4 for explanation.

RR, Relative risk; CI, confidence interval.

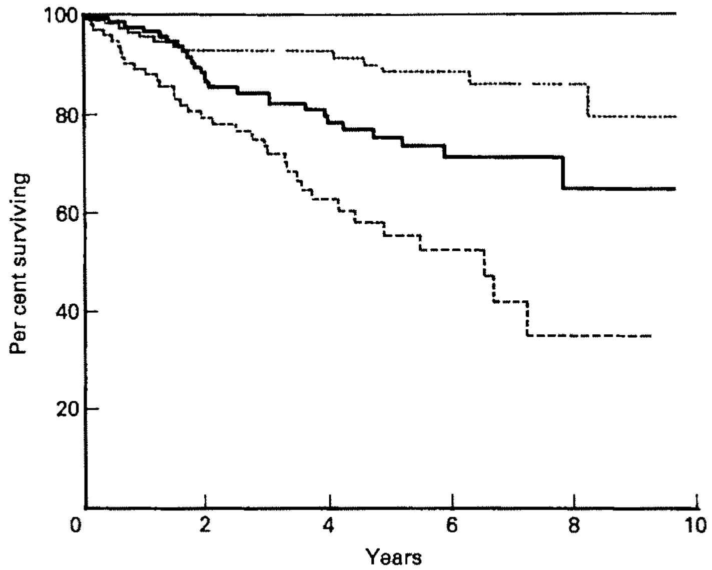

Fig. 2. Survival rate by age. ——, 1–49 years ($n = 22$); . . ., 50–59 ($n = 114$); ____, 60–69 ($n = 116$); - - -, 70 plus ($n = 94$); $P<0{\cdot}0001$.

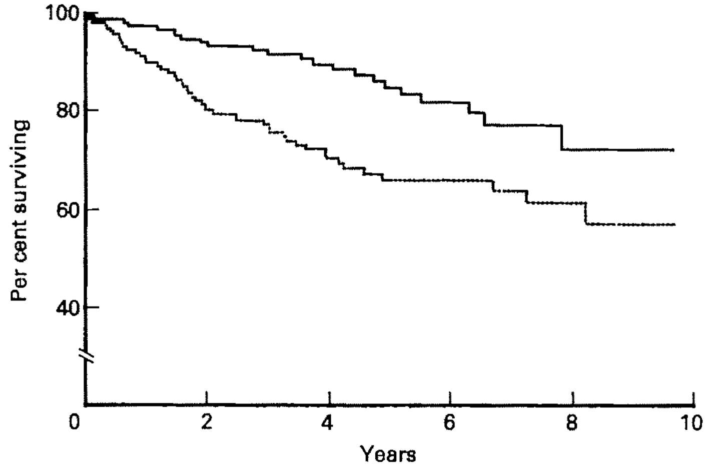

Fig. 3. Survival rate by depth of muscle invasion. ——, $<\frac{1}{2}$ ($n = 159$); . . ., $\geq\frac{1}{2}$ ($n = 166$); $P = 0{\cdot}0007$.

radiosensitivity of involved pelvic glands for postoperative irradiation. The subsequent sustained progestogenic milieu should have reduced the opportunity for further growth of latent cancer cells.

In the event there was no statistically significant difference between the groups in survival, whether one looks at the whole series or after removal of withdrawals (Fig. 1).

It has been suggested that progestational agents should be given to all patients with endometrial carcinoma from the time of the first curettage until some months after the definitive operation and radiotherapy have been completed (Taylor 1979). In a trial of 120 patients with Stage I tumours randomized to various treatments, Bonte *et al.* (1978) gave 1 mg MPA per week before and after radium packing and hysterectomy and claimed 'nearly' 100% 5-year survival in patients given progestogen and only 72% in those not given progestogen.

However, other randomized trials have shown no specific benefit from treatment with progestogens. Lewis *et al.* (1974) gave intramuscu-

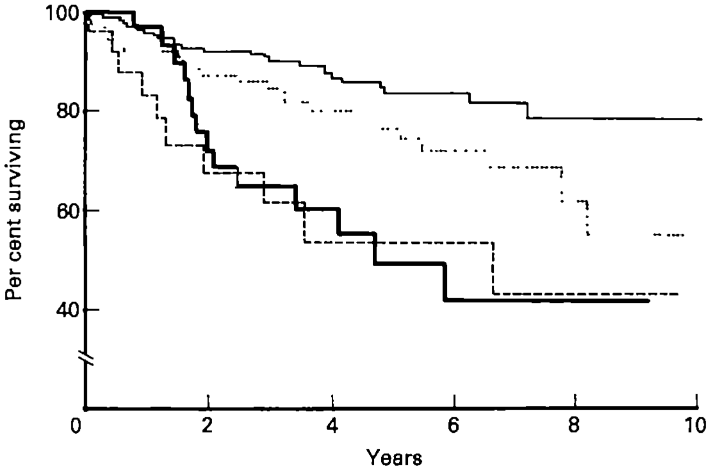

Fig. 4. Survival rate by FIGO stage. ——, Stage IA ($n = 197$); . ., Stage IB ($n = 88$); ——, Stage II ($n = 35$); - - -, Stage III ($n = 26$); $P<0{\cdot}0001$.

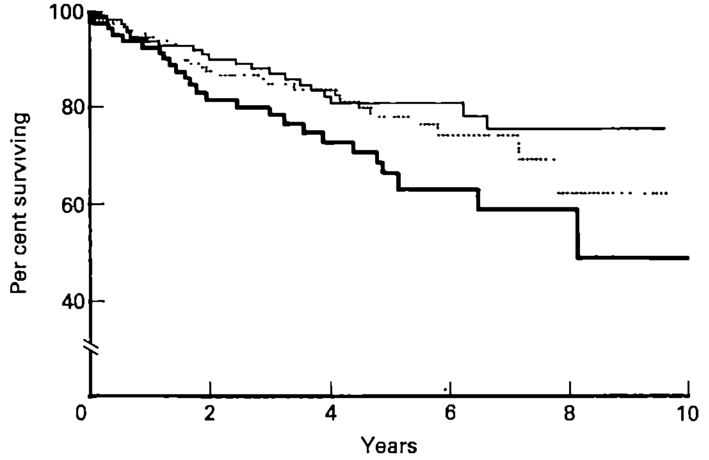

Fig. 5. Survival rate by differentiation. ——, Well ($n = 125$); . . , moderate ($n = 133$); ——, poor/anaplastic ($n = 87$); $P = 0.0190$.

lar MPA for 14 weeks as adjuvant therapy in the primary definitive treatment and found no difference between 285 treated and 287 control (placebo) patients with Stage I disease. Malkasian & Dechar (1978) gave 1000 mg of 6 methyl-17 alpha hydroxyprogesterone acetate intramuscularly within 24 h of surgery and then 500 mg weekly for 14 weeks to 18 patients with Stage I disease; some patients were also given radiotherapy but there was no difference in outcome compared with 17 control patients.

Table 6. Cardiovascular deaths

	Progestogen group	Control group
Postoperative pulmonary embolism	2	–
Myocardial infarction	2	6
Cerebrovascular accident	3	2
Total	7	8

Despite the relatively high dose of MPA initially (300 mg daily for the first year after operation) there were remarkably few side-effects in our study. Although the drug was discontinued in eight patients because of rising blood pressure, there was no overall difference in blood pressure between the two groups at 5 years.

The projected overall 5-year survival rate at 76% is better than the national average. This might be due in part to the extra interest and care generated by the trial, but the improvement over previous results might also be due to better radiotherapy with the high energy radiation to the pelvic glands.

There has been much debate about selecting patients for hormone treatment on the basis of the progesterone receptor content of the tumour, and we are currently analysing our own material. But patients with well-differentiated high-receptor-content tumours achieve the best results in any case (Creasman *et al.* 1985; Kauppila *et al.* 1982) and it would be very difficult to prove additional benefit when the drug is given as part of the primary treatment.

So contrary to our expectations the trial has shown no benefit from treatment with progestogens in addition to surgery and radiotherapy. In a way the fascinating question is why the progestogens have not helped. Perhaps the drug simply selects out unresponsive cells like bacteriological resistance to an antibiotic, or perhaps the cells become unresponsive with continued therapy. We have found no difference in the survival of patients in the two arms of the trial despite allowing for known prognostic factors and it seems unlikely that any similar regimen or drug would give a different result. What the study has demonstrated is the value of a randomized controlled trial.

Further reductions in death rates from endometrial carcinoma seem likely to come from prevention rather than from refinement of current treatment.

Conclusions and recommendations

Progestogens are expensive and not entirely harmless. In the absence of any evidence that they are of benefit as part of the primary treatment of endometrial carcinoma we suggest that their use be reserved for recurrent lesions and for patients unsuitable or unfit for surgery, situations in which their value has been established.

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References

Bokhman, J. V , Chepick, O. F., Volkova, A. T. & Vishnevsky, A S. (1985) Can primary endometrial carcinoma Stage I be cured without surgery and radiation therapy? *Gynecol Oncol* **20,** 139-155.

Bonte, J., Decoster, J. M., Ide, P & Billiet, G (1978) Hormonoprophylaxis and hormonotherapy in the treatment of endometrial adenocarcinoma by means of medroxyprogesterone acetate *Gynecol Oncol* **6,** 60-75

Braunstein, G D. (1984) The benefits of oestrogen to the menopausal woman outweigh the risks of developing endometrial cancer Opinion *CA* **34,** 210-219.

Creasman, W T., Soper, J T., McCarty, K. S. Jr, McCarty, K. S. Sr, Hinshaw, W. & Clark-Pearson, D L. (1985) Influence of cytoplasmic steroid receptor content on prognosis of early stage endometrial carcinoma. *Am J Obstet Gynecol* **151,** 922-932

Dobbie, B M. W (1953) Vaginal recurrences in carcinoma of the body of the uterus and their prevention by radium therapy. *J Obstet Gynaecol Br Emp* **60,** 702-705.

Joslin, C. A (1986) The place for radiotherapy in endometrial cancer. In *Gynaecological Oncology* (Morrow, C. P & Smart, G E., eds), Springer Verlag, Berlin, pp. 137-146.

Joslin, C A. & Thorogood, J. (1986) *Report for the Year 1985, including Cancer Statistics for 1978–83 Leeds*. Yorkshire Regional Cancer Registry, Leeds.

Joslin, C. A , Vaishampayam, G. V. & Mallik, A. (1977) The treatment of early cancer of the corpus uteri *Br J Radiol* **50,** 38-45.

Kauppila, A., Kujansuu, E. & Vihko, R (1982) Cytosol estrogen and progestin receptors in endometrial carcinoma of patients treated with surgery, radiotherapy and progestin Clinical correlates. *Cancer* **50,** 2157-2162.

Lewis, B V., Stallworthy, J. A. & Cowdell, R. (1970) Adenocarcinoma of the body of the uterus. *J Obstet Gynaecol Br Commonw* **77,** 343-348

Lewis, G. C , Slack, N H., Mortel, R. & Boon, D. J (1974) Adjuvant progestogen therapy in the primary definitive treatment of endometrial cancer. *Gynecol Oncol* **2**, 368-376.

Macdonald, R. R (1973) Progestogen therapy—The clinician's dilemma. In *Endometrial Cancer* (Brush, M. G., Taylor, R. W. & Williams, D. C., eds) Heinemann Medical Books Ltd, London, pp 212-217.

Malkasian, G D. & Dechar, D G. (1978) Adjuvant progesterone therapy for Stage I endometrial carcinoma. *Int J Gynaecol Obstet* **16**, 48-49.

Peto, R., Pike, M. C., Armitage, P. *et al.* (1977) Design and analysis of randomised clinical trials requiring prolonged observation of each patient. *Br J Cancer* **35**, 1-39.

Taylor, R. W. (1975) Hormone therapy in gynaecological cancer. In *Gynaecological Malignancy, Clinical and Experimental Studies* (Brush, M. G. & Taylor, R. W., eds) Baillière Tindall, London, pp. 212-221.

Taylor, R. W. (1979) Gynaecological malignancy. *Practitioner* **222**, 195-201.

Thornton, J J., Brown, L. A., Wells, M. & Scott, J S. (1985) Primary treatment of endometrial cancer with progestogen alone (Letter). *Lancet* **ii**, 207-208.

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Psychosexual trauma of an abnormal cervical smear

M. J. CAMPION, J. R. BROWN, D. J. MCCANCE, W. ATIA, R. EDWARDS, J. CUZICK, A. SINGER

Summary. The psychosexual sequelae of diagnosis and treatment of pre-invasive cervical atypia were assessed in three groups of women. The first group included 30 women referred to a colposcopy clinic with an abnormal cervical smear indicating cervical intraepithelial neoplasia (CIN), the second comprised 50 women who were traced as sexual partners of men with penile human papillomavirus (HPV) infection; 26 of them had histologically proven cervical atypia and 24 had no such evidence. The third group included 25 women traced as partners of men with non-specific urethritis and who did not have cervical disease. Before and after questionnaires assessed six aspects of sexual behaviour and responses before diagnosis and 6 months after treatment in women with cervical atypia. These were compared with answers given by women investigated and treated, if necessary, as partners of men with sexually transmitted disease (control group). There were statistically significant adverse psychosexual sequelae associated with diagnosis and treatment of pre-invasive cervical epithelial disease.

The clinical profile of cervical neoplasia has changed dramatically in the UK over the past two decades. Whilst overall mortality from cervical cancer has continued to decline at 1% per year since the introduction of widespread cytological screening, deaths from cervical cancer in young women under the age of 35 have increased by a factor of three (Draper & Cook 1983). When it occurs in younger women cervical carcinoma is frequently a highly anaplastic tumour and the 5-year survival for early cervical cancer has fallen to 50% for women under 35 years of age (Ward *et al.* 1985). At the same time, diagnosis of pre-invasive cervical neoplasia has increased at least three-fold over the past two decades (Wolfendale *et al.* 1983) with the attendant threat of future increases in cervical cancer mortality (Beral & Booth 1986). The modal age of diagnosis of cervical intraepithelial neoplasia (CIN) has fallen to 24 years (Singer *et al.* 1984) and the progressive potential of pre-invasive disease has become more apparent, often within a short time (Campion *et al.* 1986). Recent research has strongly implicated certain sexually transmitted types of human papillomavirus (HPV) in cervical carcinogenesis (Singer & McCance 1985) and the role of the male sexual consort in the aetiology of the disease has become more apparent (Campion *et al.* 1985).

This grim change in the clinical pattern of cervical neoplasia, the sexually transmitted

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Royal Northern Hospital, London N7 6LD
M. J. CAMPION *Research Fellow*
W. ATIA *Consultant in Genito-urinary Medicine*
A. SINGER *Consultant Gynaecologist*

Concord Repatriation Hospital, Concord, New South Wales, Australia
J. R. BROWN *Intern*

Department of Microbiology, United Medical and Dental Schools, Guy's Campus, London SE1 9RT
D. J. MCCANCE *Senior Lecturer*

Department of Mathematics, Statistics and Epidemiology, Imperial Cancer Research Fund, Lincolns Inn Fields, London WC2A 3PX
J CUZICK *Head*
R. EDWARDS *Research Officer*

Correspondence: J. Cuzick

nature of the disease and the awareness of a high-risk male who places his sexual partners at an increased risk of cervical neoplasia have recently received extensive media attention. Thus the finding of an abnormal cervical smear, the diagnosis of cervical neoplasia and treatment of the disease is associated with considerable anxiety in relation to causation, prognosis, implications of therapy, future fertility and sexual function, particularly in young women. The purpose of this study was to assess the psychosexual effects of the diagnosis and treatment of CIN and to provide an empirical foundation for subsequent psychosexual counselling in a colposcopy clinic, should such appear necessary. There were no prior hypotheses about possible psychosexual effects of investigation and treatment of an abnormal cervical smear.

Subjects and methods

Four groups of women were recruited for study.

Group 1 comprised 30 women referred to the Islington District Colposcopy Clinic, Royal Northern Hospital, London, with an abnormal cervical smear. For each woman, histology of a colposcopically directed biopsy confirmed CIN with associated HPV infection according to criteria defined by Dyson *et al.* (1984). Of the 30 women, 5 had CIN I, 7 had CIN II and 18 had CIN III with histological evidence of HPV infection reported in each.

Group 2 comprised 50 women who were called to a genito-urinary medicine clinic as the regular sexual partner of a man with penile condylomata acuminata. None gave a history of an abnormal cervical smear. Of the 50 women, 26 (52%) had pre-invasive cervical disease, either HPV infection alone or both CIN and HPV infection, confirmed on histology of a colposcopically directed biopsy. The final histological diagnoses for women in the control group were HPV infection alone in 5, CIN I in 10, CIN II in 4 and CIN III in 7 women.

Thus group 2 was divided into two subgroups: group 2(a) comprised 26 women with histologically confirmed cervical HPV infection alone or CIN with associated HPV infection, each referred as the regular sexual consort of a male with genital condylomata acuminata. Eight of the 26 women also had lower genital tract condylomata acuminata. Group 2(b) comprised the remaining 24 who were traced as the regular sexual consort of a male with penile condylomata acuminata (but who showed no cytological nor colposcopic evidence of cervical disease). Seven of these 24 women had lower genital tract condylomata acuminata.

Group 3 comprised 25 women of similar age who were referred to a genito-urinary medicine clinic as the regular sexual partner of a male diagnosed as having non-specific urethritis. None of these women had cytological or colposcopic evidence of pre-invasive cervical disease, but inflammatory changes consistent with genital tract infection were detected in the cervical smears of 8 (32%). In each woman the inflammatory atypia was cleared with appropriate antibiotic treatment.

Clinical methods

A detailed medical, obstetric, gynaecological, social and sexual history was obtained from each woman at the time of initial presentation. Complete physical and pelvic examinations were performed. Urethral, high vaginal and endocervical swabs were taken from each woman for light microscopy and culture to exclude *Candida* spp., *Trichomonas* spp., *Gardnerella vaginalis, Chlamydia trachomatis* and *Neisseria gonorrhoeae*. A cervical smear was taken, fixed and stained by the Papanicolaou method. A careful colposcopic examination of the cervix and lower genital tract for evidence of cervical atypia or lower genital tract HPV infection was performed. Colposcopically directed biopsies were taken from areas of cervical disease and fixed in formol sublimate for histology.

Initial questionnaire

Each patient consented to complete a questionnaire exploring six aspects of their sexual behaviour and response in the 6 months before presentation. The questionnaire was explained and administered during an interview lasting about 20 min. For each question, the women were shown a scale and asked to choose a point on the scale which best described their response.

The aspects of sexuality investigated were: (1) frequency of spontaneous sexual interest; (2) frequency of intercourse; (3) frequency of adequate vaginal lubrication and sexual arousal with intercourse; (4) frequency of orgasm with intercourse, (5) frequency of dyspareunia; (6) frequency of negative feelings towards intercourse.

For questions (1) and (2), subjects chose one point along a 7-point scale to describe the appropriate response. The following inscriptors were used: 0 = never; 1 = rarely; 2 = once a month; 3 = between 2 and 4 times a month; 4 = once a week; 5 = between 2 and 6 times a week; 6 = daily.

For questions (3) to (6) inclusive, a 5-point scale was used with the following inscriptors: 0 = never; 1 = rarely (25%); 2 = occasionally (50%); 3 = frequently (75%); 4 = usually.

Follow-up questionnaire

Patients in groups 1 and 2(a) were recalled to the Laser Clinic, Royal Northern Hospital, London for treatment of histologically proven cervical atypia using the carbon dioxide laser. There was an average delay of 7 weeks from initial presentation until laser therapy. Each woman was treated with laser vaporization under local anaesthetic as an outpatient. No woman in either group suffered complications from treatment which required re-presentation to hospital. Patients were requested to abstain from intercourse for 3 weeks after laser treatment and that the partner use a sheath for a further 3 weeks. Each woman was given an appointment for review at 6 months after therapy. At the time of this follow-up consultation, the patients were requested to complete the same questionnaire as previously. The responses were based on the 5–6 months since completion of the requested 3-week period of sexual abstinence after laser therapy.

Patients in groups 2(b) and 3 who were diagnosed as having a sexually transmitted infection received appropriate therapy. No patient required admission to hospital and each was declared free of disease within 4 weeks of initial diagnosis. After being declared free of disease, each patient was given a 5-month follow-up appointment and at this time was asked to complete the same questionnaire with reference to the previous 5–6 months.

Statistics

The responses to the questionnaires were analysed by non-parametric methods. Comparison of before and after responses within each group was done by the Wilcoxon signed rank test for paired samples. Comparison between groups of the initial response and the difference in the scale values of initial response and subsequent response was done by the Kruskal–Wallis test and the pairs of groups were compared by the Wilcoxon rank-sum test. In all cases a correction for ties was made. *P* values are based on two-sided tests.

Results

Age and sexual history for each group are summarized in Table 1. The responses of each woman to 'before' and 'after' questionnaires are summarized in Table 2. There was no indication that the initial responses of the four groups were different The Kruskal–Wallis significance levels for the six questions were 0·42, 0·13, 0·95, 0·86, 0·99, 0·50. The only pair of groups for which a significant difference in baseline response was noted was between groups 1 and 2(b) for question 2 ($P = 0{\cdot}04$) but in view of the number of comparisons this is most likely due to chance. However, clear differences were found between before and after responses and they differed according to group membership

The first study variable was spontaneous sexual interest. It is important to distinguish between spontaneous sexual interest not elicited by an approach from a sexual partner and inter-

Table 1. Characteristics of study and control groups

	Group 1 ($n = 30$)	Group 2(a) ($n = 26$)	Group 2(b) ($n = 24$)	Group 3 ($n = 25$)
Age (years)	24	23	24	22
	(19–26)	(19–25)	(18–26)	(17–25)
Number of sexual partners	6	5	4	5
	(3–8)	(2–6)	(2–8)	(2–8)
Age of coitarche	18	19	17	17
	(16–19)	(16–20)	(16–19)	(15–18)

Results are medians with interquartile range in brackets.

Table 2. Mean scale values of responses to six questions about psychosexuality before and after presentation in four groups of women

	Group 1 ($n = 30$)			Group 2a ($n = 26$)			Group 2b ($n = 24$)			Group 3 ($n = 25$)		
Question	Before	After	*P*	Before	After	*P*	Before	After	*P*	Before	After	*P*
1 Spontaneous interest	3·73 (0·21)	2·20 (0·19)	<0·001	3·27 (0·22)	1·92 (0·22)	<0·001	3·38 (0·22)	3·21 (0·18)	0·26	3·28 (0·23)	3·16 (0·16)	0·37
2 Frequency	3·90 (0·24)	2·27 (0·23)	<0·001	3·54 (0·15)	2·27 (0·27)	<0·001	3·25 (0·25)	3·71 (0·21)	0·07	3·72 (0·24)	3·80 (0·16)	0·74
3 Arousal	3·07 (0·16)	2·00 (0·15)	<0·001	3·23 (0·13)	2.42 (0·19)	0·001	3·21 (0·13)	3·25 (0·12)	0·75	3·16 (0·14)	3·16 (0·13)	1·00
4 Orgasm	2·50 (0·20)	1·17 (0·09)	<0·001	2·73 (0·20)	1·50 (0·22)	<0·001	2·67 (0·17)	2·71 (0·17)	0·79	2·60 (0·20)	2·64 (0·16)	0·74
5 Discomfort	0·47 (0·12)	1·30 (0·23)	0·004	0·50 (0·14)	1·69 (0·24)	<0·001	0·46 (0·13)	0·52 (0·15)	0·63	0·56 (0·16)	0·48 (0·12)	0·66
6 Negative feelings	0·20 (0·07)	2·27 (0·16)	<0·001	0·35 (0·11)	2·15 (0·23)	<0·001	0·46 (0·13)	0·42 (0·17)	0·92	0·36 (0·13)	0·36 (0·14)	1·00

Results are mean (SE) scale values.

Significance of difference between before and after in each group assessed by Wilcoxon signed rank test

est arising once sexual interaction with the partner begins. This crucial distinction was explained before completion of the questionnaire. The dampening of spontaneous sexual interest in groups 1 and 2(a) was apparent after diagnosis and treatment of cervical pre-invasive disease, the scale values were significantly depressed after treatment ($P<0·001$ for each group). Follow-up assessment of women in groups 2(b) and 3 demonstrated no significant change ($P = 0·26$ and 0·37 respectively). The differences between the before and after scores are clearly greater in groups 1 and 2(a) than in groups 2(b) and 3 (Table 3).

Frequency of intercourse, adequacy of vaginal lubrication and sexual arousal and frequency of orgasm were then assessed as measures of sexual function and response. Again diagnosis and treatment of pre-invasive cervical atypia were associated with significant decrease in each variable but there was no change in the control groups, 2(b) and 3, despite being referred as the sexual partners of males with a diagnosed sexually transmitted infection. A marked depression was seen in the scores of women in groups 1 and 2(a). However, there was no significant differences between groups 1 and 2(a) at either interview, i.e. the indication for referral for investigation of cervical atypia did not appear to influence sexual behaviour or response. The differences between groups 1 and 2(a) and groups 2(b) and 3 are again highly statistically significant (Table 3).

Table 3. Mann–Whitney significance levels for differences in 'before minus after scores' between all possible pairs of the four groups for each of six questions Mann–Whitney for each question for all group pairs—*P* values (based on before-after differences)

	Group 2a	Group 2b	Group 3
Question 1			
1	0·47	<0·001	<0·001
2a		<0·001	<0·001
2b			0·81
Question 2			
1	0·17	<0·001	<0·001
2a		<0·001	<0·001
2b			0·31
Question 3			
1	0·22	<0·001	<0·001
2a		<0·001	0·003
2b			0·71
Question 4			
1	0·59	<0·001	<0·001
2a		<0·001	<0·001
2b			0·98
Question 5			
1	0·29	0·05	0·01
2a		<0·001	<0·001
2b			0·48
Question 6			
1	0·68	<0·001	<0·001
2a		<0·001	<0·001
2b			0·70

Discomfort experienced during intercourse or dyspareunia was the fifth variable studied. No distinction was made between superficial and deep dyspareunia. For both groups 1 and 2(a) there was a tendency towards increased discomfort with intercourse after diagnosis and treatment of cervical atypia ($P = 0·004$ and $<0·001$ respectively). There was no significant difference between before and after responses for groups 2(b) and 3 ($P = 0·63$ and 0·66 respectively). This is despite the fact that seven women in group 2(b) required chemotherapy or laser treatment for vulval condylomata acuminata.

To assess the woman's feelings towards her partner and, in particular, towards the sexual aspects of the relationship, she was asked to nominate the frequency of negative feelings towards sexual intercourse with her current partner. For women who were not in a regular sexual relationship, the question was directed at feelings towards sexual intercourse generally rather than with any specific partner. In groups 1 and 2(a) there was a significant increase in the frequency of negative feelings towards sexual intercourse ($P<0·001$ in each case). Women in group 2(a) who had been referred specifically as the sexual partners of men with penile condylomata acuminata and who had been diagnosed as having an abnormal cervix did not, as a group, show more hostile feelings towards sexual intercourse or towards their partners than women referred with an abnormal smear (group 1). Negative feelings towards sexual intercourse were not increased among women with a healthy cervix, investigated as the sexual partners of men with sexually transmitted diseases ($P = 0·92$ and 1·00 for groups 2(b) and 3 respectively). Groups 1 and 2(a) were found to be similar in their response ($P = 0·68$) as were groups 2(b) and 3 ($P = 0·70$). However, the difference between groups 1 and 2(a) and groups

2(b) and 3 were highly significant ($P<0.001$ in each comparison).

Discussion

Genital neoplasia threatens not only a woman's life but her self concept, body image and sexuality. It is not surprising therefore that the finding of an abnormal cervical smear and the diagnosis of pre-invasive cervical neoplasia is the source of considerable anxiety, particularly for the young woman. In addition to presenting the threat of cancer with attendant implications of drastic therapy and poor prognosis, the diagnosis has implications for future fertility, child bearing capacity and sexual function. There are no significant studies to date which provide information regarding the psychosexual problems faced by women diagnosed as having cervical intraepithelial neoplasia and the sexual adjustment of these women after treatment.

In this study, women referred to the Colposcopy Clinic with an abnormal cervical smear showed no differences in sexual behaviour and attitude in the 6 months before presentation compared with control groups. This was despite the fact that the abnormal smear was often detected 6–12 weeks before presentation and, in six cases, there had been at least a 2-year history of abnormal cervical smears. However, after colposcopic examination, biopsy of the atypical cervical transformation zone and laser vaporization of histologically proven pre-invasive disease, this study has demonstrated significant changes in the patients' attitude towards sex and towards their sexual partners, as well as in their sexual behaviour and response.

The decreased spontaneous sexual interest among women treated for CIN is important as studies of patients with psychosexual problems indicate relative independence of sexual interest and sexual response (Bancroft *et al.* 1982). The consistent deleterious effect of diagnosis and treatment of CIN upon sexual behaviour and response is demonstrated in the significantly decreased frequency of intercourse, decreased vaginal lubrication and sexual arousal and decreased frequency of orgasm in groups 1 and 2(a) compared with groups 2(b) and 3. This may be a response to anxiety particularly in relation to potential harmful effects of sexual intercourse after treatment, but the associated decrease in spontaneous sexual interest suggests a more profound effect upon the woman's self concept and body image following diagnosis and treatment of CIN.

A significant increase in negative feelings towards sexual intercourse or towards a regular sexual partner amongst women treated for cervical pre-malignancy is also demonstrated in this study A similar response was not evident in the control groups of women with a normal cervix, but who were investigated as the sexual partners of men with a sexually transmitted infection. Anxiety may cause decreased sexual arousal, inadequate lubrication and difficulty with orgasm. Sexual intercourse becomes uncomfortable or less enjoyable, propagating negative feelings. Additionally, women in groups 1 and 2(a) frequently developed hostility directed towards a sexual partner or towards sexual intercourse Hence negative feelings seemed to be aroused by both anxiety and hostility. The tendency towards discomfort with intercourse following treatment for CIN also appeared to relate to anxiety and diminished sexual response.

This study has demonstrated a significant alteration in sexual attitudes, behaviour and response in young women after diagnosis and treatment of pre-invasive cervical disease. The women were frequently in regular relationships or married and the social implications of these findings are obvious and important. Psychosexual problems after major surgery for gynaecological malignancy are readily understood due to substantial genital change, reduced pelvic and genital sensitivity, sexual arousal deficits and significant disruption of body image (Anderson & Hacker 1983). This is associated with decreased frequency of activity, low sexual arousal, sexual anxiety and limited sexual satisfaction. However, the altered attitudes towards sexuality and altered sexual behaviour following conservative treatment of pre-invasive gynaecological disease is not readily explained by these factors.

This study was undertaken in a relatively homogeneous North London population and the conservative treatment offered was the CO_2 laser. Whilst the results may differ with population and with type of treatment, the study exposes significant psychosexual trauma associated with diagnosis and treatment of CIN.

Women presenting with an abnormal cervical smear are generally young, sexually active, fertile women. Sexuality profoundly influences body image and self concept. The threat posed to life, fertility and future child-bearing by the diagnosis of CIN is a source of anxiety which influences most aspects of the woman's sexual attitudes and response. The progressive potential of pre-invasive cervical disease (McIndoe *et al.* 1984), including mild atypia (Evans & Monaghan 1985; Campion *et al.* 1986), is becoming apparent. This mandates appropriate investigation, treatment and follow-up of an abnormal cervical smear despite the findings of this study, but there is also a need for supportive and informative counselling. It is important that information is available and proffered at each clinic visit to minimize anxiety and the attendant adverse psychosexual sequelae. A further study to assess the effects of counselling in decreasing anxiety associated with diagnosis and treatment of pre-invasive cervical disease is required.

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References

Andersen, B. L. & Hacker, N P. (1983) Psychosexual adjustment after vulvar surgery. *Obstet Gynecol* **62**, 457-462.

Bancroft, J., Tyrer, G. & Warner, R. (1982) The classification of sexual problems in women. *Br J Sex Med* **9**, 30-37

Beral, V. & Booth, M. (1986) Prediction of cervical cancer incidence and mortality in England and Wales. *Lancet* **i**, 495.

Campion, M J., Singer, A., Clarkson, P K. & McCance, D. J. (1985) Increased risk of cervical neoplasia in consorts of men with penile condylomata acuminata. *Lancet* **i**, 943-946.

Campion, M. J., McCance, D. J , Cuzick, J & Singer, A. (1986) Progressive potential of mild cervical atypia. a prospective cytological, colposcopic and virological study. *Lancet* **i**, 237-240.

Draper, G. J. & Cook, G. A. (1983) Changing patterns of cervical cancer rates. *Br Med J* **287**, 510-512.

Dyson, J. L., Walker, P. G. & Singer, A. (1984) Human papillomavirus infection of the uterine cervix: histological appearances in 28 cases identified by immunocytochemical techniques. *J Clin Pathol* **37**, 126-130.

Evans, A. S. & Monaghan, J. M. (1985) Spontaneous resolution of cervical warty dysplasia. the relevance of clinical and nuclear DNA features a prospective study. *Br J Obstet Gynaecol* **92**, 165-169.

McIndoe, W. A , McLean, M. R., Jones, R. W. & Mullins, P. R. (1984) The invasive potential of carcinoma *in situ* of the cervix. *Obstet Gynecol* **64**, 451-456.

Singer, A., Walker, P , Tay, S. K & Dyson, J. (1984) Impact of introduction of colposcopy to a district general hospital. *Br Med J* **289**, 1049-1051.

Singer, A. & McCance, D. J (1985) The wart virus and genital neoplasia: a casual or causal association. Commentary. *Br J Obstet Gynaecol* **92**, 1083-1085.

Ward, B G., Shepherd, J. H. & Monaghan, J. M. (1985) Occult advanced cervical cancer. *Br Med J* **290**, 1301-1302.

Wolfendale, M. R., King, S. & Usherwood, M. McD. (1983) Abnormal cervical smears: are we in for an epidemic? *Br Med J* **287**, 526-528

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Genital virus infection and cervical neoplasia

HENRY C. KITCHENER

Summary. The reported association between genital infection by herpes simplex virus (HSV) type 2 and cervical neoplasia has been investigated at a molecular level. Tissue culture of over 50 cervical cancers resulted in the development of several cell lines but none of these expressed HSV information. The permanent cell line, Cx106, which was generated was found to contain multiple genome copies of human papillomavirus (HPV) type 16. Southern blot analysis of nine cervical cancers showed an authentic 2·8 Kb fragment of HSV-2 DNA in one of the tumours. This piece of viral DNA maps in a morphological transforming region of the HSV genome. Superinfection of cervical cancers with temperature-sensitive (ts) mutants of HSV 1 and 2 did not generate recombinant virus, suggesting that HSV DNA was not present in the tumours studied. An attempt to identify latent HSV close to the cervix in organ cultures of uterosacral ligament tissues resulted in reactivation of virus in several instances. These results are discussed against a background of decline in acceptance by many, for the HSV link with cervical cancer, and the dramatic impact of the discovery of a close relation between HPV type 16 and lower genital tract neoplasia.

Cervical cancer has come to be regarded almost as a venereal disease. Rigoni-Stern's classic observation 150 years ago that married women developed uterine cancer more frequently than single women was the first suggestion that cervical cancer was related to sexual activity. Conversely the rarity of the disease in nuns (Gagnon 1950) reveals that virginity provides a degree of protection probably afforded to no other human cancer. More refined studies in recent years demonstrated that the principal risk factors for developing cervical neoplasia are early age of first intercourse, and multiple sex partners (Rotkin 1967, 1973) and a promiscuous husband (Buckley *et al.* 1981), all of which imply that venereal transmission of some mutagenic agent triggers malignant change in the metaplastic cells of the transformation zone.

The obvious possibilities in this regard include some intrinsic constituent of seminal fluid or an extrinsic transmitted organism. Of the latter the principal contenders are the two DNA viruses which commonly infect the cervix, the herpes virus, herpes simplex virus (HSV) and the papova virus, human papillomavirus (HPV). In nature, the herpes virus, Marek disease virus, produces lymphoid cancer in chickens, and the Shope papillomavirus produces epidermoid cancers in cottontail rabbits.

HSV and cervical neoplasia

HSV, a double-stranded DNA virus of molecular weight 10^8 daltons, infects the lower genital tract in the form of two serotypes, HSV-2 being twice as common as HSV-1 (Smith *et al.* 1976). The linear model of the HSV genome is ascribed 100 map co-ordinates which are used to designate the positions of subgenomic fragments (Fig. 1). After infection of a cell by HSV, the viral DNA is transcribed into RNA, followed by

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Department of Midwifery, University of Glasgow, The Queen Mother's Hospital, Yorkhill, Glasgow G3 8SH
HENRY C KITCHENER *Senior Registrar*

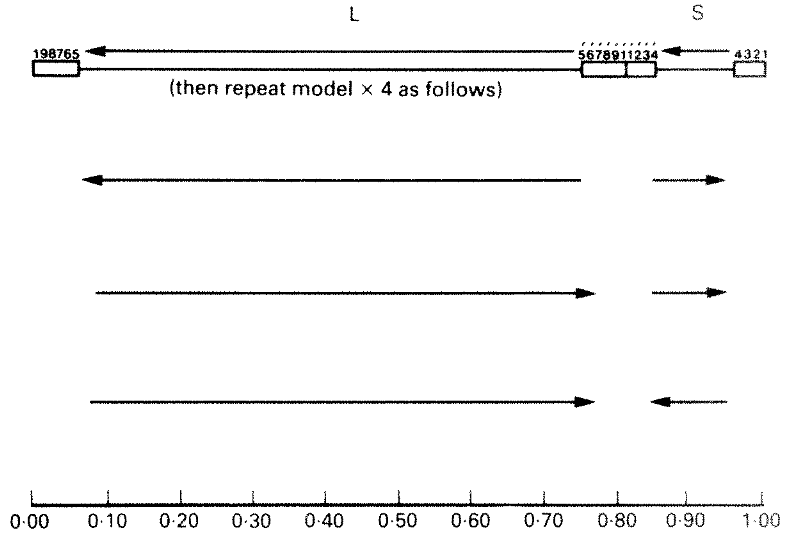

Fig. 1. The linear model proposed for the HSV genome (Sheldrick & Berthelot 1974) comprising a unique long and short segment each flanked by terminal repeat sequences. Of the four possible isomers one orientation is designated the prototype and is by convention subdivided into 100 equal segments so that location on the genome can refer to map coordinates between 0·00 and 1·00.

translation on host cell ribosomes into immediate and early proteins necessary for replication of the viral genome and a range of late proteins required to complete the assembly and packaging of progeny virus. After resolution of the acute infection, latency and reactivation are responsible for recurrent attacks. One of the most significant properties of HSV is its ability, when inactivated, to transform mammalian cells. These transformed cells, which are tumorigenic, contain HSV specific DNA (Frenkel *et al.* 1976), RNA (Collard *et al.* 1973) and proteins (Duff & Rapp 1971). HSV DNA alone can transform cells when transfected; as indeed can subgenomic fragments known as the morphological transforming regions 1 and 2 (Reyes *et al.* 1979).

The initial link in the 1960s between HSV-2 and cervical neoplasia was based on finding a higher prevalence of CIN in women whose smears showed indications of HSV infection (Naib *et al.* 1966). This was consolidated by finding an increased incidence of pre-invasive and invasive cervical neoplasia in subjects with serological evidence of previous HSV-2 infection (Rawls *et al.* 1968). Because an association of this kind may be due simply to confounding covariables such as promiscuity, research was directed at identifying virus-specified products within the neoplastic cells.

Positive immunochemical studies using HSV specific antibodies (Royston & Aurelian 1970; Dreesman *et al.* 1980) appeared to indicate viral expression in at least 40% of cervical neoplastic tissues. The advent of the in-situ hybridization technique (Jones *et al.* 1978) permitted identification of viral RNA complementary to DNA probes. Several studies showed the presence of transcripts complementary to HSV-2 DNA (McDougall *et al.* 1980, 1982; Eglin *et al.* 1981; Maitland *et al.* 1981) but only Eglin *et al.* (1981) had internal controls of normal cervical tissue. The absence of viral message in these normal control tissues appeared to indicate an exclusive association of the viral probe with the neoplastic cells, although there was concern about the specificity of the hybridization when homogeneity between HSV and human DNA sequences was discovered (Peden *et al.* 1982). The advent of Southern blotting (Southern 1975) permitted the sensitive and specific identification of virus DNA sequences in cellular DNA. Previously there had been only one unconfirmed report of HSV DNA in cervical cancer tissue (Frenkel *et al.* 1972).

With this background several types of experiment were undertaken to try to understand more fully what relation exists between HSV and host cells in cervical neoplasia.

Tissue culture of neoplastic cervical epithelium

Although about a dozen permanent cell lines of cervical cancer have been reported none of these was known to express viral information at the time this study was started. The technique used in these studies for culturing cervical cancer tissues was that of explantation; the method of enzyme dissociation was tried but was unsuccessful. Fragments of freshly obtained tumour were explanted into 50 mm petri dishes containing 40% Ham F12 medium and 40% Dulbecco minimal essential medium enriched with 20% fetal calf serum, epidermal growth factor (EGF) (10 ng/ml) and hydrocortisone (0·4 μg/ml). Within 2–3 days a monolayer of epithelial cells grew out from the explant. These cells had a large nucleocytoplasmic ratio and electron microscopy showed desmosomes and tonofilaments, indicating cells of squamous epithelial origin. Of some 50 tumours, around half produced short-term cell culture; the rest which failed to grow were largely necrotic, infected lesions.

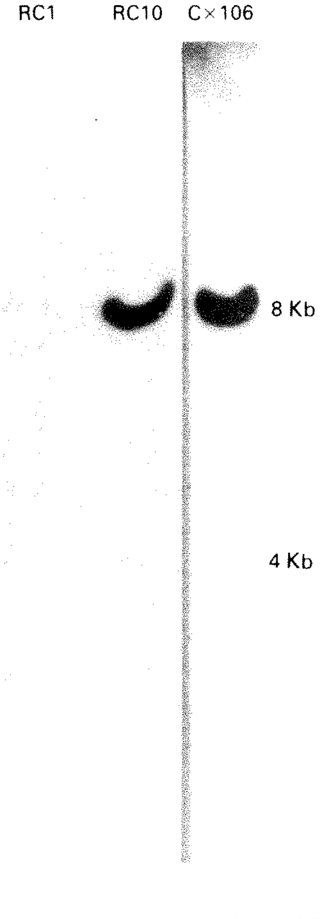

Fig. 2. An autoradiograph of Bam H1 digested DNA extracted from the cervical carcinoma cell line Cx106 hybridized to HPV-16 DNA. The viral probe was released from the plasmid vector and purified twice with agarose gel electrophoresis. The Cx106 DNA can be seen clearly to contain an 8 kilobase fragment with comigrates with the HPV-16 DNA reconstruction and the band intensity corresponds with that of the reconstruction containing the equivalent of 10 genome copies per cell.

Although contamination was not a major problem, subculture was difficult and only three cell lines survived to 10 passages with just one (Cx106) being established in culture as a permanent line. Cx106 possesses the characteristics of a neoplastic cell line; it is tumorigenic in athymic nude mice and produces colonies in sloppy agar. Interestingly, having been generated in the presence of EGF, it remains EGF dependent. This suggests some selection process during the early stages of culture. Karyology studies by Giemsa banding show the cell line to be hypotetraploid with a modal chromosome number of 72, and no evidence of Hela marker chromosomes (Nelson Rees *et al.* 1975). Extensive testing, including Southern blotting (DNA/DNA hybridization) analysis for HSV DNA, has revealed no evidence of HSV-specified products in the cells. However, DNA/DNA hybridization against an HPV-16 DNA probe (kindly performed by J. C. M. Macnab) has demonstrated the presence of HPV-16 genomes (Fig. 2) at a frequency of 10 genome copies per cell (H. C. Kitchener & J. C. M. Macnab, unpublished data). The HPV DNA appears to be stably integrated being present at similar copy numbers at various passages.

DNA/DNA hybridization

Using Southern blotting (Southern 1975), cervical carcinomas were studied for the presence of HSV-2 genomes (Park *et al.* 1983). The method used was standard, great care being taken to excise the plasmid vector in which the HSV DNA probes were cloned thus avoiding non-specific hybridization between vector and cellular sequences. Nine cervical cancers were studied, eight squamous and one adenocarcinoma and control tissues included normal cervix, tissues of sites of potential HSV infection as well as other normal and transformed cells where HSV was not expected. None of the tissues contained infectious virus. The DNAs extracted from the tissues were digested with the endonuclease Hind III and following gel electrophoresis the DNAs were blotted against the viral DNA probes which between them carried 80% of the HSV genome. Only one blot was positive against the probe Bgl IIn; this was an adenocarcinoma (Cx122). By further blot analyses involving digests by the restriction enzymes Bam H1 and Xhol and the DNA probe Bgl IIn, an authentic HSV fragment of 2·8 Kb was identified (Fig. 3) which maps in the morphological transforming region 2.

Although the numbers are small, the previous in-situ hybridization data suggested that there should have been more HSV-positive tumours. Either the blotting technique was insufficiently sensitive (<0·1 genome copy per cell) to detect very small amounts of viral DNA or the tumours did not contain HSV DNA. This could be because they had never been infected with HSV or because, following infection, a 'hit and run' event involving the HSV genome had occurred. Analysis of a larger number of lower genital tract cancers (Macnab *et al.* 1985) has revealed that 9% contain HSV genome. Finding HSV DNA from a transforming region of the genome in the DNA of a human cervical cancer is clearly important but, as a finding in isolation, its significance is not clear. Failing to find HSV genomes in cervical cancers does not preclude HSV from having been involved in the initiation process, because HSV DNA is not necessary to maintain the transformed phenotype in HSV transformed cells (Minson *et al.* 1976).

Superinfection of cervical carcinomas by temperature-sensitive HSV mutants

Temperature-sensitive (ts) mutants are viruses which have been mutagenized and selected such that they grow at a permissive temperature (PT), e.g. 31°C, but not at the non-permissive temperature (NPT), e.g. 38°C (Subak-Sharpe 1969). Such mutants can detect virus gene functions in HSV-transformed cells by complementation, indicated by an increased yield when assayed at the PT following superinfection at the NPT (Macnab & Timbury 1976). The significance of such complementation was confirmed when Park *et al.* (1980) were able to demonstrate intertypic recombination resulting from virus superinfection of ts HSV-transformed cells, indicating unambiguously the presence of viral DNA in the transformed cells.

This approach was exploited to investigate cervical cancers for the presence of HSV functions. Fragments of malignant and normal cervi-

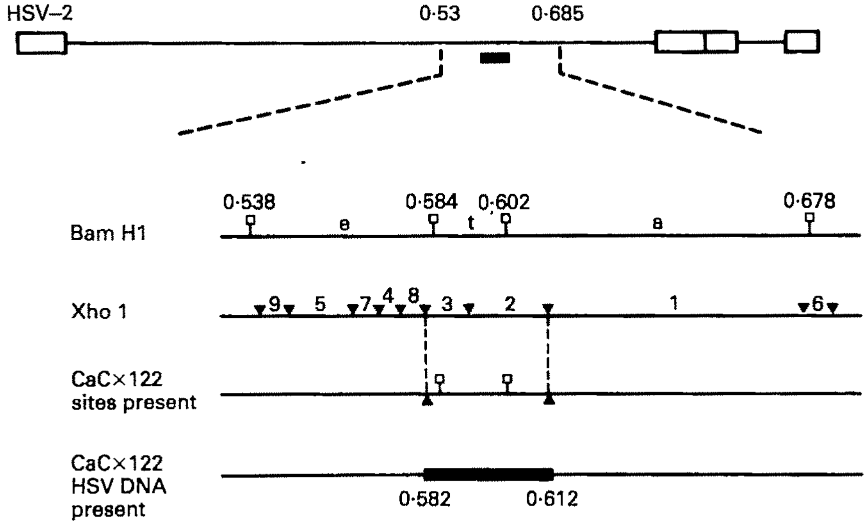

Fig. 3. Schematic enlargement of the HSV-2 genome sequence 0·53–0·68 showing the cleavage site of Bam H1 (□) and Xho (▼). The sequence indicated (0·582–0·612) which was detected in Cx122 includes the Xho 2 and 3 fragments which correspond to Bam H1t with some extension into Bam H1e and Bam H1a fragments. The morphological transforming region 2 extends from 0·582–0·628 (Park *et al* 1983).

cal tissues were used to stimulate as closely as possible an in-vivo model system which would not be as subject to the selection problems of derived cell cultures. The method involved chopping the tissues to be superinfected into fragments about 1 mm across. A 100 mg sample of tissue was incubated for 1 h with 10^6 plaque-forming units of a variety of ts mutants of HSV of both types 1 and 2. The inoculum was then removed and 2 ml of culture medium (described previously) were added. The infected tissues were incubated at 31°C and 38°C for 3 and 2 days respectively. The tissues were then sonicated in the medium and the virus yield assayed on baby hamster kidney cells (Fig. 4).

Preliminary experiments had demonstrated that this experimental system could produce a productive HSV infection of similar yields in both normal and cancerous cervical biopsies by both ts and wild type virus (Fig. 5). That the tissues had been infected was further proven by identifying radiolabelled HSV polypeptides by polyacrylamide gel electrophoresis of the tissues (Kitchener 1983).

Fourteen squamous cervical cancers each with an external normal cervical control were separately superinfected at both 31°C and 38°C with a range of ts mutants of both HSV-1 and 2. No virus except the wild type control was yielded when assayed at the NPT of 38°C, which indicated an absence of recombination. Following superinfection at the NPT a six-fold or greater yield by the cancer (X^c) over the control (X^n) was taken to indicate positive complementation. It can be seen from Table 1 that there was a range of frequency of complementation of the various ts mutants.

In the absence of recombination these positive results cannot be assumed to indicate HSV gene functions in the cervical cancers. It is also unlikely that the positive results were merely an artefact of the experimental system because none of the control tissues attained the complementation index and duplicate superinfection yielded reproducible results. It seems more likely that certain host cell functions, for example an oncogene product or other proteins either exclusive to or over-expressed in the cancer cells, could facilitate replication of the mutants.

HSV latency in uterosacral ligaments

In an effort to identify HSV latency closer to the cervix than in the pelvic dorsal root ganglia (Baringer 1974), studies were performed on the uterosacral ligament (Kitchener *et al.* 1982). This structure was selected as it runs from the presacral surface, where the nerve plexuses are situated, to the uterus just above the level of the internal os.

Uterosacral ligaments were obtained at Wertheim's hysterectomy from 19 patients with cervical cancer and from 11 patients having a simple total hysterectomy for benign uterine disease. Briefly, the uterosacral tissue was explanted into culture medium and incubated for up to 14 days. After this, the tissue was sonicated to release any infectious virus which was tested for on baby hamster kidney indicator cells. Five of the 19 specimens from cancer patients yielded HSV (four were HSV-2 and one was HSV-1) and one of the benign specimens yielded HSV-2.

The possible source of latency was thought to be autonomic ganglia. This was investigated by

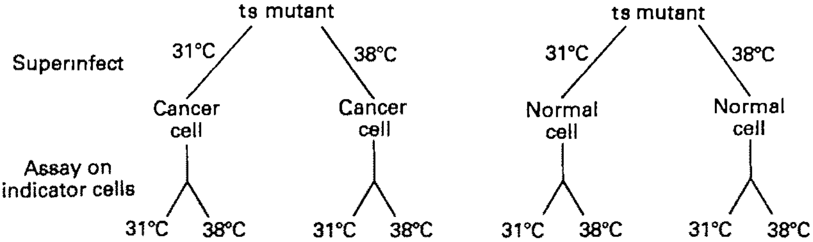

Fig. 4. A flow chart of the superinfection experiment When the cancer tissue which was superinfected with ts mutants of HSV-1 and 2 at 38°C (non-permissive temperature) yielded a significantly greater yield over correspondingly infected normal cervical tissues when assayed on indicator cells at 31°C (permissive temperature), this was taken as positive complementation. Any virus yielded when assayed at 38°C (non-permissive temperature) is either recombinant or revertant (wild type virus).

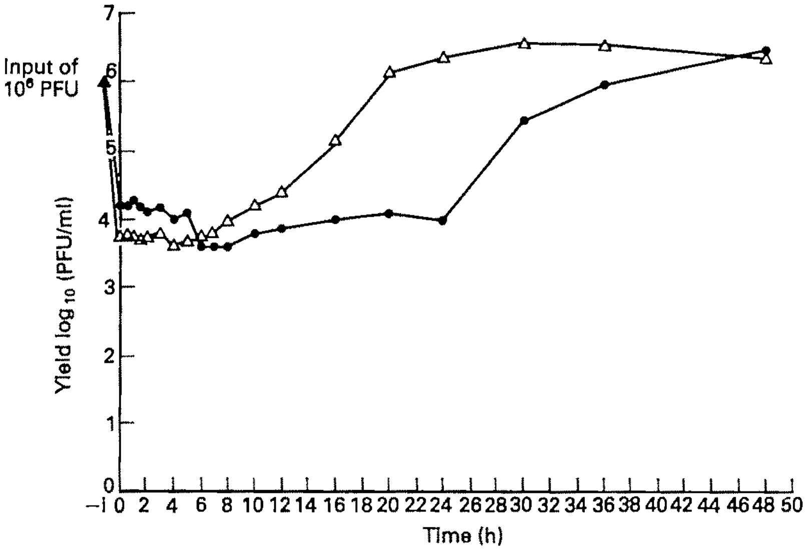

Fig. 5. Virus growth curve in fragments of cervical cancer (●) and normal cervical tissue (△) following inoculation with 10^6 plaque-forming units of HSV-1. Following inoculation the virus was washed off and the tissues incubated until the various times shown (h). They were then frozen, sonicated and assayed. Such infection produces similar yields after 48 h in both cancer and normal cervical tissues.

serially sectioning uterosacral ligaments at 20-μm intervals throughout their length, and in 2 of 8 ligaments, autonomic ganglia were found. Although by no means certain, it is possible that these ganglia are the reservoir of latency. The proximity of latent virus may be important for recurrent infection and this may apply equally to other parts of the lower genital tract.

Table 1. The frequency of positive complementation, $X^c/X^n > 6$, of various ts mutants of HSV-1 and HSV-2 following superinfection of cervical cancer, X^c and X^n represent the yield when assayed at 31°C following superinfection at 38°C for cervical cancer and normal cervix respectively

ts Mutant	Positive complementation
A syn +	3/7
B syn +	4/7
D syn +	2/3
E syn +	7/13
G syn +	5/12
H syn +	1/5
K syn +	8/13
S syn +	1/5
ts 1	3/4
ts 9	2/3
ts 12	3/5
ts 13	1/1

Comments

It is apparent from the Southern blotting results and also the absence of recombinants in the superinfection experiments that HSV DNA is present in only a few cervical neoplasms. This seems contrary to the reports of a few years ago that indicated HSV-specified antigens and RNA were identified in at least 30–40% of cervical cancers. Although HSV DNA may remain undetected due to lack of sensitivity, there is the possibility that some of the positive results for other products in earlier studies were not HSV specific. Mention has been made of the HSV DNA homology with human DNA, suggesting that this could have led to false positive results in the in-situ hybridization though the internal controls of Eglin *et al.* (1981) should have prevented this. This is not perhaps dissimilar to the situation in the superinfection studies where the results may be reflecting host cell function rather than virus expression. This experience emphasizes the general importance of internal controls in increasing the certainty with which these experimental results can be interpreted particularly regarding the 'causal' or 'casual' relation between an infectious agent and a disease. Many workers are now sceptical of an important relation between herpes virus infection and cervical cancer. Although the evidence is conflicting, the matter will not be resolved until greater insight is gained into the molecular biological events involved in viral transformation, as well as into the extrinsic influences which may act as cofactors. The lack of a close clinical association between previous genital herpes infection and subsequent development of cervical neoplasia is a negative aspect of the HSV hypothesis, but this is certainly not the case for the human papillomavirus (HPV) which appears to be producing an epidemic of genital infection.

HPV and cervical neoplasia

Any discussion of cervical cancer is currently dominated by its association with HPV infection. HPV causes a wide range of human cutaneous lesions including erythrodysplasia verruciformis, a rare warty disease, which gives rise to malignant lesions in 25% of affected individuals. In nature the Shope papillomavirus causes papillomatous disease (Shope & Hurst 1933) in cottontail rabbits in the Mississippi Basin and some of these lesions progress via dysplasia to epidermoid cancer over 1–2 years which has an obvious parallel with cervical cancer. These data make the virus responsible for genital warts an agent that must also be taken seriously when considering cervical carcinogenesis. Subtypes of HPV, of which over 30 have been identified, are differentiated on the basis of the DNA restriction profile. The HPV subtypes express common antigens which can be identified readily using immunochemical staining.

The observations of Meisels & Fortin (1976) and Meisels *et al.* (1977) resulted in the cytological, histological and colposcopic descriptions of atypical flat cervical warts. Many of these lesions are indistinguishable from pure CIN colposcopically. That HPV is present in these condylomas has been demonstrated by electron microscopy (Reid *et al.* 1980), immunohistochemistry (Morin *et al.* 1981), and Southern blotting (Gissman *et al.* 1982). These lesions have a widespread geographical distribution and are not confined to Western societies (Durst *et al.* 1983; Sutherland *et al.* 1986), the means of spread being both male and female promiscuity. Although the natural history of these koilocytotic lesions with dysplastic features is not understood as well as that of 'pure' CIN, many authorities regard it as artificial to distinguish between warty and non-warty CIN, and from a therapeutic point of view they are generally treated in the same way.

The past few years have seen much effort put into probing both pre-invasive and invasive lesions using Southern blot analysis in order to identify the HPV subtypes associated with various grades of pathology. HPV-6, originally identified in condylomata acuminata (Gissman & zur Hausen 1980), is mainly identified in low grade CIN whereas HPV-16 has been identified in high grade CIN (CIN 3) and in invasive lesions (Crum *et al.* 1984; McCance *et al.* 1985). Campion *et al.* (1986) observed that lesions which progress from low grade to high grade CIN contained HPV-16, although the degree of CIN at the beginning of the study was not histologically assessed. The same group (McCance *et al.* 1985) have suggested that the detection of HPV DNA in multifocal intraepithelial neoplasia of the lower female genital tract is further evidence that genital cancer is causally related to HPV infection.

Compelling as the evidence may appear, the case for HPV being causally related to cervical cancer is not yet proven. HPV-16 DNA is also present in a significant proportion of histologically normal cervical tissue in both the presence and absence of CIN (J. Murdoch, personal communication) and has been identified in normal tissue up to 5 cm distant from squamous genital tumours (Macnab *et al.* 1986). The question must be asked: what relevance has HPV to malignancy in these cases? More knowledge is required of the prevalence of HPV in normal tissues and of the natural history of such infection together with the role of other risk factors such as smoking (Harris *et al.* 1980) before definite statements about the cause of cervical cancer can be made. Although cell cultures of genital cancers are tedious to generate, lines such as Cx106 may yield a valuable model system for studying viral expression as well as integration sites. Another area of study could involve the effects of potential cofactors, e.g. hormones on cell growth.

There is no reason to doubt that the classic initiation/promotion model of carcinogenesis proposed by Berenblum (1941) applies to cervical carcinogenesis with its well-recognized precancerous phase lasting several years or more. Such a model implies a multifactorial aetiology, rather than a single agent, such as HPV, being alone responsible for the development of the neoplastic process. It would appear that viral agents do have a role, either as an initiating or promoting factor but that other factors such as environmental carcinogens, hormones, host immunity, and even retroviruses, could also have important influences. Finding the viral footprints has begged many questions that remain unanswered.

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The HPV-16 DNA probe was the kind gift of H. zur Hausen.

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References

Baringer, J. R. (1974) Recovery of herpes simplex virus from human sacral ganglia. *New Engl J Med* **291,** 828-830.

Berenblum, I (1941) The mechanism of carcinogenesis. *Cancer Res* **1,** 807-815

Buckley, J D., Harris, R. W. C., Doll, R , Vessey, M. P. & Williams, P T. (1981) Case control study of the husbands of women with dysplasia or carcinoma of the cervix uteri *Lancet* **ii,** 1010-1014.

Campion, M. J., McCance, D J , Cuzick, J & Singer, A. (1986) Progressive potential of mild cervical atypia. prospective cytological colposcopic and virological study. *Lancet* **ii,** 237-240.

Collard, W., Thornton, H. & Green, M. (1973) Cells transformed by human herpesvirus type 2 transcribe virus-specific RNA sequences shared by herpesvirus types 1 and 2. *Nature* **234,** 264-266.

Crum, C P., Ikenberg, H., Richart, R M. & Gissman, L. (1984) Human papillomavirus type 16 and early cervical neoplasia. *New Engl J Med* **310,** 880-883.

Dreesman, G. R , Burek, J., Adam, E., Kaufman, R. H., Powell, K L. & Melnick, J. L (1980) Expression of herpes virus-induced antigens in human cervical cancer. *Nature* **238,** 591-593.

Duff, R. G. & Rapp, F. (1971) Oncogenic transformation of hamster cells after exposure to herpes simplex virus type 2. *Nature* **233,** 48-50.

Durst, M., Gissman, L., Ikenberg, H. & zur Hausen, H. (1983) A papillomavirus DNA from a cervical carcinoma and its prevalence in cancer biopsy samples from different geographic regions *Proc Natl Acad Sci USA* **80,** 3812-3815

Eglin, R. P., Sharp, F., Maclean, A B., Macnab, J C M., Clements, J. B & Wilkie, N. M. (1981) The detection of RNA complementary to herpes simplex virus DNA in human cervical squamous cell neoplasms. *Cancer Res* **41,** 3597-3606.

Frenkel, N., Roizman, B., Cassai, E. & Nahmias, A J. (1972) A DNA fragment of herpes simplex virus 2 and its transcription in human cervical cancer tissue. *Proc Natl Acad Sci USA* **69,** 3784-3789.

Frenkel, N., Locker, M., Cox, B., Roizman, B. & Rapp, F (1976) Herpes simplex virus DNA in transformed cells: sequence complexity in five hamster cell lines and one derived hamster tumor *J Virol* **18,** 885-893.

Gagnon, F. (1950) Contribution to the study of the etiology and prevention of cancer of the cervix of the uterus. *Am J Obstet Gynecol* **60,** 516-527

Gissman, L & zur Hausen, H. (1980) Partial characterisation of viral DNA from human genital warts (condylomata acuminata). *Int J Cancer* **25,** 605-609.

Gissman, L., Villiers, E. M. & zur Hausen, H (1982) Analysis of human genital warts (condyloma acuminata) and other genital tumours for human papillomavirus type 6 DNA *Int J Cancer* **29,** 143-146.

Harris, R. W C., Brinton, L A., Cowdell, R. H., Skegg, D C. G , Smith, P. G., Vessey, M P. & Doll, R (1980) Characteristics of women with dysplasia and carcinoma *in situ* of the cervix uteri *Br J Cancer* **42,** 359-369.

Jones, K. W., Fenoglio, C. M., Shevchuk-Chaban, M., Maitland, N. & McDougall, J. K. (1978) Detection of herpes simplex virus type 2 in RNA in human cervical biopsies by *in situ* hybridization. In

Oncogenesis and Herpes Virus III (de The, G., Herle, W & Rapp, F., eds) IARC, Lyon, Part 2, pp. 917-925.

Kitchener, H C , Cordiner, J. W & Eglin, R. P. (1982) Latency of herpes simplex virus in uterosacral ligaments. *Am J Obstet Gynecol* **143,** 839-840.

Kitchener, H. C. (1983) Studies at a molecular level of the association between herpes simplex virus type 2 and cervical neoplasia. MD Thesis, Glasgow University

Macnab, J. C. M., Park, M , Cameron, I R., Kitchener, H. C., Walkinshaw, S. A , McLaughlan, J , Davidson, M. J., Cordiner, J. W., Clements, J B & Subak-Sharpe, J. H. (1985) Possibilities and consequences of virus detection in patients with CIN and cancer. *Cancer Campaign, Vol. 8,* Fischer Verlag, Stuttgart, New York, pp. 151-160.

Macnab, J C. M. & Timbury, M. C. (1976) Complementation of ts mutants by a herpes simplex virus ts transformed cell line. *Nature* **261,** 233-235.

Macnab, J. C. M., Walkinshaw, S. A., Cordiner, J W. & Clements, J. B. (1986) Human paillomavirus in clinically and histologically normal tissue of patients with genital cancer. *New Engl J Med* **315,** 1052-1058.

McCance, D J., Clarkson, P. K , Walker, P. G. & Singer, A. (1985) Human papillomavirus types 6 and 16 in multifocal intraepithelial neoplasias of the female lower genital tract. *Br J Obstet Gynaecol* **92,** 1093-1100

McDougall, J. K., Galloway, D A. & Fenoglio, C M. (1980) Cervical carcinoma: detection of herpes simplex virus RNA in cells undergoing neoplastic change. *Int J Cancer* **25,** 1-8.

McDougall, J. K , Crum, P. C., Fenoglio, C. M., Goldstein, L. C & Galloway, D. A (1982) Herpesvirus-specific RNA and protein in carcinoma of the uterine cervix. *Proc Natl Acad Sci USA* **79,** 3853-3857.

Maitland, N., Kinross, J. H., Busuttil, A., Ludgate, S. M., Smart, G. E & Jones, K. W. (1981) The detection of DNA tumour virus-specific RNA sequences in abnormal human cervical biopsies by *in situ* hybridization *J Gen Virol* **55,** 123-137

Meisels, A. & Fortin, R (1976) Condylomatous lesions of the cervix and vagina I. Cytologic patterns. *Acta Cytol* **20,** 505-509

Meisels, A., Fortin, R. & Roy, M. (1977) Condylomatous lesions of the cervix: cytologic, colposcopic and histopathologic study. *Acta Cytol* **21,** 379-390

Meisels, A., Roy, M , Fortier, M , Morin, C., Casas Cordero, M., Shah, K. V. & Turgeon, H. (1981) Human papillomavirus infection of the cervix The atypical condyloma. *Acta Cytol* **25,** 7-16.

Minson, A. C., Thouless, M. E., Eglin, R. P & Darby, G (1976) The detection of virus DNA sequences in a herpes type 2 transformed hamster cell line. *Int J Cancer* **17,** 493-510

Morin, C., Braun, L , Casas Cordero, M., Shah, K. V., Roy, M , Fortier, M. & Meisels, A. (1981) Confirmation of the papillomavirus etiology of condylomatous cervical lesions by the peroxidase-antiperoxidase technique *J Natl Cancer Inst* **66,** 831-835

Naib, Z. M., Nahmias, A. J. & Josey, W. E. (1966) Cytology and histopathology of cervical herpes simplex infection. *Cancer* **19,** 1026-1031.

Nelson-Rees, W. A , Flandermayor, R. R. & Hawthorne, P. K (1975) Distinctive banded marker chromosomes of human tumour cell lines. *Int J Cancer* **16,** 74-82.

Park, M., Lonsdale, D. M., Timbury, M C , Subak-Sharpe, J. H. & Macnab, J. C. M. (1980) Genetic retrieval of viral genome sequences from herpes simplex virus transformed cells. *Nature* **285,** 412-415.

Park, M., Kitchener, H C. & Macnab, J. C. M (1983) Detection of herpes simplex virus type 2 DNA restriction fragments in human cervical carcinoma tissue *EMBO J* **2,** 417-422

Peden, K., Mounts, P. & Hayward, G. S. (1982) Homology between mammalian cell DNA sequences and human herpes virus genomes detected by a hybridization procedure with high complexity probe. *Cell* **31,** 71-80.

Rawls, W. E., Tomkins, W. A. F., Figueroa, M. E. & Melnick, J. L. (1968) Herpes virus type 2. Association with carcinoma of the cervix. *Science* **161,** 1255-1256.

Reid, R., Laverty, C R., Coppleson, M., Isarangkul, W & Hills, E. (1980) Non-condylomatous cervical wart virus infection. *Obstet Gynecol* **55,** 476-483.

Reyes, G. R., La Femina, R., Hayward, S D & Hayward, G. S. (1979) Morphological transformation by DNA fragments of human herpes viruses Evidence for two distinct transforming regions in herpes simplex virus types 1 and 2 and lack of correlation with biochemical transfer of the thymidine kinase gene. *Cold Spring Harbor Symp Quant Biol* **44,** 629-641.

Rotkin, I. D. (1967) Adolescent coitus and cervical cancer. association of related events with increased risk. *Cancer Res* **27,** 603-617.

Rotkin, I. D. (1973) A comparison review of key epidemiological studies in cervical cancer related to current searches for transmissable agents *Cancer Res* **33,** 1353-1367.

Royston, I. & Aurelian, L. (1970) Immunofluorescent detection of herpes simplex virus antigens in exfoliated cells from human cervical carcinoma. *Proc Natl Acad Sci USA* **67,** 204-212.

Sheldrick, P. & Berthelot, N. (1974) Inverted repetitions in the chromosomes of herpes simplex virus. *Cold Spring Harbor Symp Quant Biol* **39,** 667-678.

Shope, R. E. & Hurst, E. W (1933) Infectious papillomatosis of rabbits *J Exp Med* **58,** 607-624

Smith, I. W , Pautherer, I F. & Robertson, D M M (1976) Serological studies in genital herpes. *Lancet* **ii,** 1086.

Southern, E. M. (1975) Detection of specific sequences among DNA fragments separated by gel electrophoresis. *J Mol Biol* **98,** 503-517.

Subak-Sharpe, J. H. (1969) *Proceedings of the First International Congress for Virology. Helsinki 1968* Karger, Basel, p. 252.

Sutherland, I H., Arulkumaran, S. & Kitchener, H. C. (1986) Atypical condylomas of the cervix uteri in Singapore women: A histopathological and immunohistochemical study. *Aust NZ J Obstet Gynaecol* **26,** 151-154

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Treatment of menstrually induced acute intermittent porphyria by a long-acting gonadotrophin-releasing hormone agonist (D Trp^6-Pro^9 N ethylamide) LHRH. Case report

R. J. NORMAN, J. MILLER, R. P. MILLAR, S. M. JOUBERT

Case report

A 24-year-old receptionist with a positive family history of acute intermittent porphyria (AIP) was first seen in 1982. Her father had been diagnosed as having AIP and her aunt died after a presumed acute porphyric attack. The patient's menarche was at 12 years after which there were irregular menstrual periods. At 17 years she developed occasional bouts of abdominal pain but had an uneventful pregnancy the following year. At 19 years acute attacks occurred a few days before her periods, at first intermittently but subsequently with every menstrual period necessitating frequent hospital admissions and narcotic analgesia. There was no history of oral contraception, abnormal dietary habits or ingestion of drugs known to exacerbate AIP. There was a history of moderate ingestion of alcohol. She did not develop photosensitivity or any other skin lesions.

D Trp^6-Pro^9-GnRH ethylamide was synthesized by Dr Milton (MRC Regulatory Peptide Unit, Cape Town) and was injected daily by the patient (initially 400 μg daily decreasing to 200 μg daily). Luteinizing hormone (LH), follicle stimulating hormone (FSH), prolactin, oestradiol (E_2) and progesterone were measured daily for 4 days, weekly for a month and monthly thereafter as described previously (Norman *et al.* 1981, 1986).

AIP was confirmed during a period of remission by measurement of urine amino laevulinic acid (ALA) (17·9 μg/ml, reference range <5 μg/ml), porphobilinogen (11 μg/ml, reference range <5 μg/ml) and red blood cell porphobilinogen deaminase activity (21·5 nmol/l, reference range 20·7–62·5 nmol/ml RBC). Urinary total porphyrins and stool porphyrins were in the reference range.

Therapy with a gonadotrophin releasing hormone (GnRH) agonist led to an initial increase in LH, FSH, E_2, and prolactin (Fig. 1) as expected by the stimulatory effect of this agonist. Two weeks after commencement the patient suffered an attack. Within a month, sex hormone levels were suppressed and hypo-oestrogenism ensued. There were two further AIP attacks during the next 12 months, both mild. One resulted from the patient not taking her medication for 2 days and the second after excessive alcohol intake. She had no further menstrual periods and suffered hot flushes which she considered minor. Breast size diminished but there was no vaginal dryness or dyspareunia. Overall, the patient was very happy with the results. Repeat measurement of urinary ALA and porphobilinogen (PBG) showed no significant changes from pretreatment values (PBG 12 μg/ml, ALA 16 μg/ml).

Discussion

Acute intermittent porphyria (AIP) is an autosomal dominantly inherited disorder which presents clinically with acute abdominal pain and neuropsychiatric symptoms (Tschudy &

MRC Preclinical Diagnostic Chemistry Research Unit, Department of Chemical Pathology, University of Natal Medical School, PO Box 17039, Congella 4013, Republic of South Africa
R. J. NORMAN *Professor*
S. M. JOUBERT *Professor*

MRC Regulatory Peptide Unit, Department of Chemical Pathology, University of Cape Town Medical School, Observatory 7925, Republic of South Africa
R. P. MILLAR *Professor*

Durdoc Centre, Durban, Republic of South Africa
J. MILLER

Correspondence: R. J. Norman

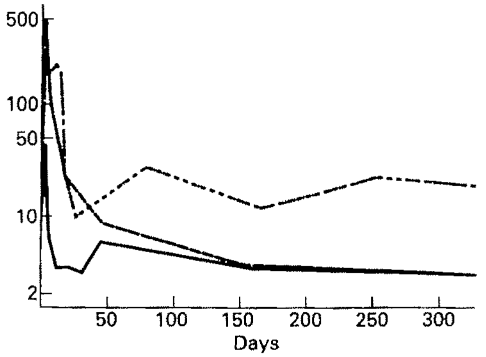

Fig. 1. LH, FSH and oestradiol levels after start of gonadotrophin releasing hormone (GnRH) therapy ———, LH (u/l); - - - FSH (u/l); — —.—, Oestradiol (pg/ml).

Lamon 1980; Kappas *et al.* 1983). The genetic basis of the disorder is a limitation of the activity of porphobilinogen deaminase (uroporphyrinogen I synthase) while the intermittent nature of the disease is due to the induction of the enzyme delta laevulinic acid synthetase (ALA synthetase) by a variety of factors including certain drugs and hormones (Tschudy & Lamon 1980). In a small group of women with AIP, acute attacks can be precipitated by cyclic hormonal changes during the menstrual cycle (Paxton *et al.* 1974; Kappas *et al.* 1983) leading to incapacitating premenstrual hospital admissions. These patients are frequently sensitive to oestrogen and progestogens in the contraceptive pill and it may be extremely difficult to abolish the hormonal changes responsible for the induction of ALA synthetase. The advent of gonadotrophin agonists and antagonists offers the potential for treating this condition and in this report we describe medical therapy of menstrually induced AIP using the agonist D-Trp^6-Pro^9-GnRH ethylamide.

Premenstrual exacerbation of AIP was completely abolished by the long-term use of a GnRH agonist in this patient. This was associated with an induction of hypo-oestrogenism following decreased gonadotrophin stimulation of the gonads The initial and inevitable stimulation of oestradiol led to an acute attack in the first 2 weeks but the two further attacks were either due to missed therapy or to other inducing agents (in this case alcohol).

It is not yet certain which of the endogenous hormones are responsible for the menstrually related prevalence of AIP in women. Androgens from the adrenals and gonads are potent stimulators of ALA synthetase (Kappas *et al.* 1983) and production may be reduced by GnRH agonist therapy (Chang *et al.* 1983) Progesterone is also important and the wide changes in this steroid in the menstrual cycle may be significant in premenstrual induction of ALA and PBG. Oestrogens are relatively poor inducers of ALA synthetase although many synthetic sex steroids may influence the production of ALA and PBG Anderson *et al* (1979) have shown that 5α reduction of steroids is significantly reduced in patients with clinically expressed AIP suggesting that 5 β steroid metabolites are important precipitating agents. Regardless of the aetiology, GnRH agonists were able to down-regulate the ovary and produce remission in our case and that of Anderson *et al.* (1984).

Agonist therapy has several advantages over traditional methods of dealing with premenstrual porphyria. It is effective, is used prophylactically, can be self-administered and is easily reversed. The disadvantages, however, are that prolonged hypo-oestrogenism can lead to osteoporosis and the initial stimulation of LH and FSH can precipitate an attack These effects could be blocked by low dose administration of oestrogen in the first case and use of antioestrogens in the second instance. The use of antagonists may be superior to that of agonists and will avoid the initial stimulation, but were not available locally at the time when treatment had to be instituted.

References

Anderson, K E , Bradlow, H L , Sassa, S & Kappas, S. (1979) Studies in porphyria VIII. Relationship of the 5α-reductive metabolism of steroid hormone to clinical expression of the genetic defect in acute intermittent porphyria *Am J Med* **66**, 644-650

Anderson, K. E., Spitz, I. M., Sassa, S , Bardin, C. W & Kappas, S. (1984) Prevention of cyclical attacks of acute intermittent porphyria with a long acting agonist of luteinizing hormone *N Engl J Med* **311**, 643-645

Chang, R J., Laufer, L R., Meldrum, D P , Defazio, J , Lu, J K H , Vale, W W , Rivier, J & Judd, H (1983) Steroid secretion in polycystic ovarian disease after ovarian suppression by a long-acting gonadotropin-releasing hormone agonist *J Clin Endocrinol Metab* **56**, 897-899

Kappas, A , Sassa, S. & Anderson, K E (1983) The Porphyrias In *The Metabolic Basis of Inherited Disease* (Stanbury, J B., Wyngaarden, J B , Fredrickson, D. S., Goldstein, J. L. & Brown, M. S., eds), McGraw-Hill, New York, pp 1301-1384

Norman, R. J., Green-Thompson, R W., Jialal, I., Soutter, W P., Pillay, N. L. & Joubert, S. M. (1981) Hyperthyroidism in trophoblastic neoplasia. *Clin Endocrinol* **15,** 395-401

Norman, R. J, Naidoo, C., Reddi, K., Vink, G. & Joubert, S. M. (1986) Endocrine studies in African women with isolated gonadotrophin-releasing hormone deficiency. *S Afr Med J* **70,** 152-155

Paxton, J. W., Moore, M. R, Beattie, A. D. & Goldberg, A. (1974) 17 Oxosteroid conjugates in plasma and urine of patients with acute intermittent porphyria *Clin Sci Mol Med* **46,** 207-222

Tschudy, D P & Lamon, J M (1980) Porphyrin metabolism and the porphyrias. In *Metabolic Control and Disease* (Bondy, P K & Rosenberg, L. E., eds), W. B. Saunders, Philadelphia, pp 939-1007.

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Fetal death *in utero* and cocaine abuse. Case report

HILARY O. D. CRITCHLEY, SHEILA M. WOODS, A. J. BARSON,
T. RICHARDSON, B. A. LIEBERMAN

Case report

An apparently healthy 17-year-old single girl in her first pregnancy had a serum alpha fetoprotein (AFP) level of 125 μg/l at 17 weeks gestation which is higher than the median plus two standard deviations. A second repeat sample also showed a raised serum AFP level of 168 μg/l. Detailed ultrasound examination revealed oligohydramnios but no fetal abnormality, and cordocentesis confirmed a normal chromosome complement. The patient was admitted at 26 weeks gestation with arrest of fetal growth and persisting oligohydramnios. Ultrasound scan suggested intrauterine growth retardation (biparietal diameter 5·72 cm, <10th centile; abdominal circumference 19 cm, 3rd centile). The fetal heart rate pattern was reactive and a biophysical profile (Manning *et al.* 1980) normal.

The evening following admission the patient developed regular uterine contractions and fetal death *in utero* was confirmed. She proceeded, without request for analgesia, to spontaneous delivery of a normal male fetus (body weight 743 g) with postural abnormality secondary to oligohydramnios. The placenta was macroscopically normal (weight 190 g).

The social history raised the suspicion of drug abuse and a full toxicological screen on fetal whole blood revealed cocaine at a concentration of 1 mg/l by gas chromatography. This was within the range (>0·9 mg/l, mean 6 mg/l; Stead & Moffat 1983) associated with fatalities in adults.

Discussion

Recent reports suggest that use of cocaine by pregnant women may influence the outcome of pregnancy. A significantly higher rate of spontaneous abortion has been observed (Chasnoff *et al.* 1985) and placental abruption described in association with cocaine usage (Acker *et al.* 1983). Fetal death *in utero* followed by spontaneous abortion where toxic levels of cocaine were demonstrated in the fetus *post mortem* has been described, but there is a dearth of information about effects of this drug on the fetus and newborn. Madden *et al.* (1986) reported a lack of symptoms, or evidence of teratogenicity, in infants whose mothers were regular cocaine abusers but appreciate the need for long-term follow-up. Studies by Moore *et al.* (1986) in the pregnant ewe and fetus have demonstrated that recreational doses of cocaine produced a reduction in uterine blood flow. The drug passed easily into the fetal circulation from the maternal blood stream and induced secondary hypertensive effects on fetal cardiovascular homeostasis.

The relation between cocaine use and the raised maternal AFP levels and oligohydramnios is unclear. It is only possible to speculate on any role played by cordocentesis in the presence of oligohydramnios and the subsequent death of this infant.

In view of increasing cocaine use worldwide, pregnant women should be made aware of the possible consequences. It may not be easy to recognize abuse and in this case no symptoms were apparent. Where use of this drug is suspected a toxicological screen should be included in the investigation of fetal loss.

St Mary's Hospital for Women and Children, Whitworth Park, Manchester M13 0JH
HILARY O. D. CRITCHLEY *Registrar in Obstetrics and Gynaecology*
SHEILA M. WOODS *Senior House Officer in Obstetrics and Gynaecology*
A. J BARSON *Consultant Paediatric Pathologist*
T. RICHARDSON *Senior Biochemist*
B. A LIEBERMAN *Consultant Obstetrician and Gynaecologist*

Correspondence Dr Hilary Critchley, Tutor in Obstetrics and Gynaecology, Hope Hospital, Eccles Old Road, Salford M6 8HD

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We wish to thank Mr K. Nicolaides of King's College Hospital, London for conducting the cordocentesis on this patient.

References

Acker, D , Sachs, B P , Tracey, K J & Wise, W E. (1983) Abruptio placentae associated with cocaine use. *Am J Obstet Gynecol* **146,** 220-221

Chasnoff, I J , Burns, W. J , Schnoll, S H & Burns, K A (1985) Cocaine use in pregnancy. *N Engl J Med* **313,** 666-669

Madden, J D., Payne, T F. & Miller, S (1986) Maternal cocaine abuse and effect on the newborn *Pediatrics* **77,** 209-211

Manning, F. A., Platt, L D & Sipos, L (1980) Antepartum fetal evaluation, development of a biophysical profile. *Am J Obstet Gynecol* **136,** 787-795.

Moore, T R , Sorg, J , Miller, L., Key, T. C & Resnik, R (1986) Hemodynamic effects of intravenous cocaine in the pregnant ewe and fetus *Am J Obstet Gynecol* **155,** 883-888.

Stead, A H. & Moffat, A. C (1983) A collection of therapeutic, toxic and fatal blood drug concentrations in man *Hum Toxicol* **3,** 437-464

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Fetal brain death. Two case reports

J. G. NIJHUIS, N. KRUYT, J. A. M. VAN WIJCK

Case reports

Patient no. 1

A healthy 26-year-old woman was admitted in her second pregnancy at 42 weeks and 5 days gestation. The first pregnancy had been uneventful and she was delivered at home of a healthy daughter weighing 3450 g. The current pregnancy had been normal until 42 weeks and 1 day when she noticed an absence of fetal movements. She was referred 4 days later. On examination her blood pressure was 130/90 mmHg, the fundal height was normal and there was no oedema or proteinuria. The fetal heart rate (FHR) recording showed a markedly fixed pattern at 160 beats/min without decelerations (Fig. 1A). Ultrasonographic investigation showed a fetus without detectable anomalies; the amount of fluid and the placenta seemed normal. No body or breathing movements were observed on several occasions. Amniotomy was performed and the fluid appeared to be a light green/brown colour. A microblood sample taken from the fetal scalp revealed normal values: pH 7·33, base-excess (BE) −2·6. The FHR recorded from a scalp-electrode is shown in Fig. 1B. After oxytocin stimulation she was delivered of a female infant weighing 3300 g in a depressed condition; it was floppy, pale, and had no spontaneous breathing. The heart rate was 60 beats/min. A blood sample from the umbilical artery was normal: pH 7·42, BE +1·6. The infant was artificially ventilated and the heart rate improved but the child did not react to external stimuli and an electroencephalogram showed no cerebral activity. The diagnosis of brain death was made and the parents agreed with the decision to stop the ventilation. The baby died 45 min later. Post-mortem examination revealed no congenital anomalies. The brain showed normal vasculature and generalized signs of anoxic damage at all levels, possibly of some days duration. There was no sign of chronic hypoxia, infection or haemorrhage. The placenta and umbilical cord were normal.

Patient no. 2

A healthy 24-year-old woman noticed spontaneous rupture of the membranes at 35 weeks and 6 days gestation in her third pregnancy. The first two pregnancies and deliveries had been uneventful: a son (2240 g) and a daughter (3120 g). The current pregnancy had progressed normally until admission. On examination clear fluid was draining through the cervix and the FHR was normal (Fig. 2A). The woman was admitted to hospital and advised to stay in bed to await spontaneous labour, although on a couple of occasions she left her bed to smoke a cigarette. After 12 h the FHR was routinely recorded again, but now showed a fixed pattern at 170 beats/min (Fig. 2B). The patient had no complaints but she was not sure if the baby had moved during the past few hours. There were no signs of infection, no prolapse of the umbilical cord, and because of absence of cervical dilatation it was not possible to take a blood sample from the fetal scalp. On ultrasound examination no abnormalities were seen, but body and breathing movements were absent. Although intrauterine brain death was considered, severe hypoxia could not be excluded. It was therefore decided to perform a caesarean section and a boy weighing 2375 g was born in the same condition as described in our first patient. A blood sample from the umbilical artery was normal: pH 7·23, P_{O_2} 15 mmHg and BE −7. The infant was ventilated but the clinical condition did not

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Department of Obstetrics and Gynaecology, Groot Ziekengasthuis, 'sHertogenbosch, The Netherlands
J. G. NIJHUIS *Registrar*

Department of Obstetrics and Gynaecology, Catharina Hospital, Eindhoven, The Netherlands
N. KRUYT *Resident*
J. A. M. VAN WIJCK *Consultant*

Correspondence: Dr J. G. Nijhuis, University Hospital Nijmegen, Department of Obstetrics and Gynaecology, PO Box 9101, 6500 HB Nijmegen, The Netherlands

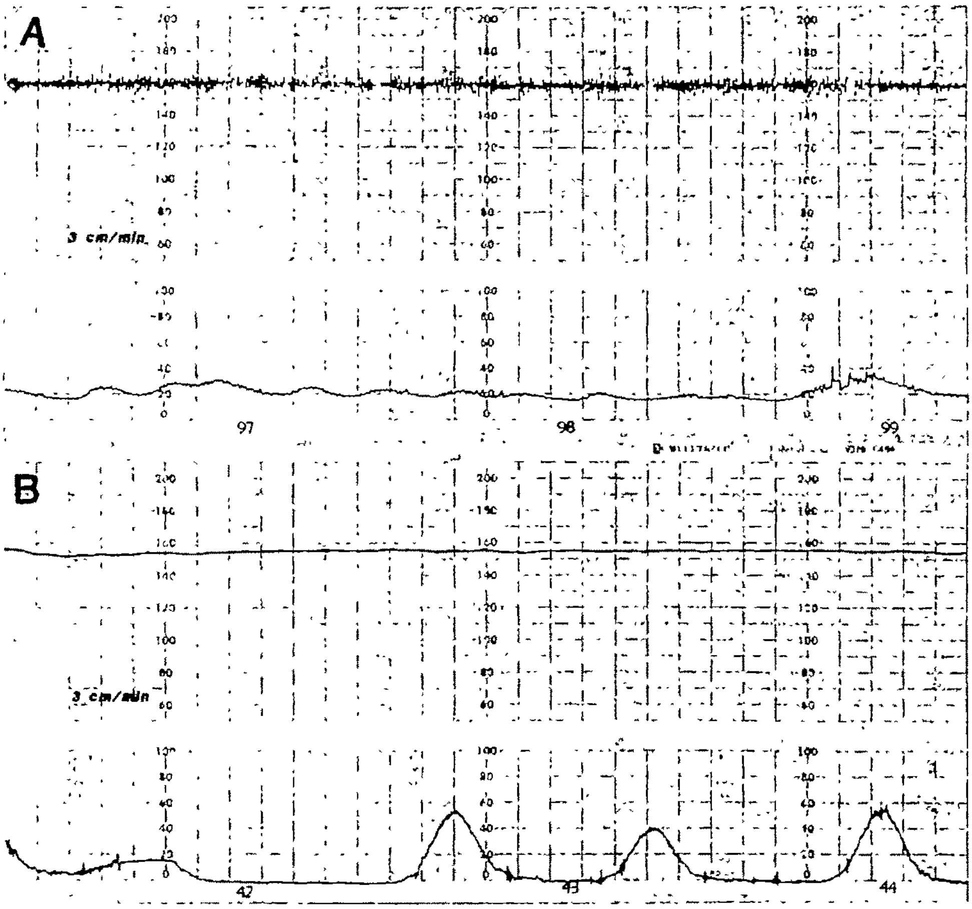

Fig. 1. Representative parts of the FHR in patient 1, recorded externally by Doppler ultrasound (A) and from a scalp-electrode (B) Paper speed 3 cm/min.

change. Ultrasonography of the brain revealed no abnormalities but an electroencephalogram showed no activity. The diagnosis of brain death was made and the parents agreed with the decision to stop the ventilation after which the baby died. A postmortem examination was refused by the parents, but the placenta and cord were normal.

Discussion

We have presented two case reports of intra-uterine brain death or fetal decerebration. In both fetuses the most likely cause of this disastrous damage to the brain was a period of hypoxia or anoxia. It could be that there had been a transient occlusion of the umbilical cord which might happen more easily if the amount of fluid were decreased. Although not confirmed by ultrasonography, this could have been the case because of postmaturity in the first patient and the ruptured membranes in the second. In both patients the diagnosis was made after birth, although most other possibilities were excluded before birth. In the second patient a diagnosis of brain death was considered, but fetal distress could not be excluded and therefore the patient was delivered by caesarean section.

To our knowledge only two cases of decerebration have been described, neither of them being unexplained. Adams *et al.* (1977) presented a case of decerebration detected during labour. In this case the amniotic fluid was strongly stained with meconium indicating that there had indeed been a period of hypoxia. Van der Moer *et al.* (1985) described a case of decerebration after maternal respiratory and cardiovascular collapse following the administration of diazepam for a serious attack of hyperventilation. Furthermore, antenatally

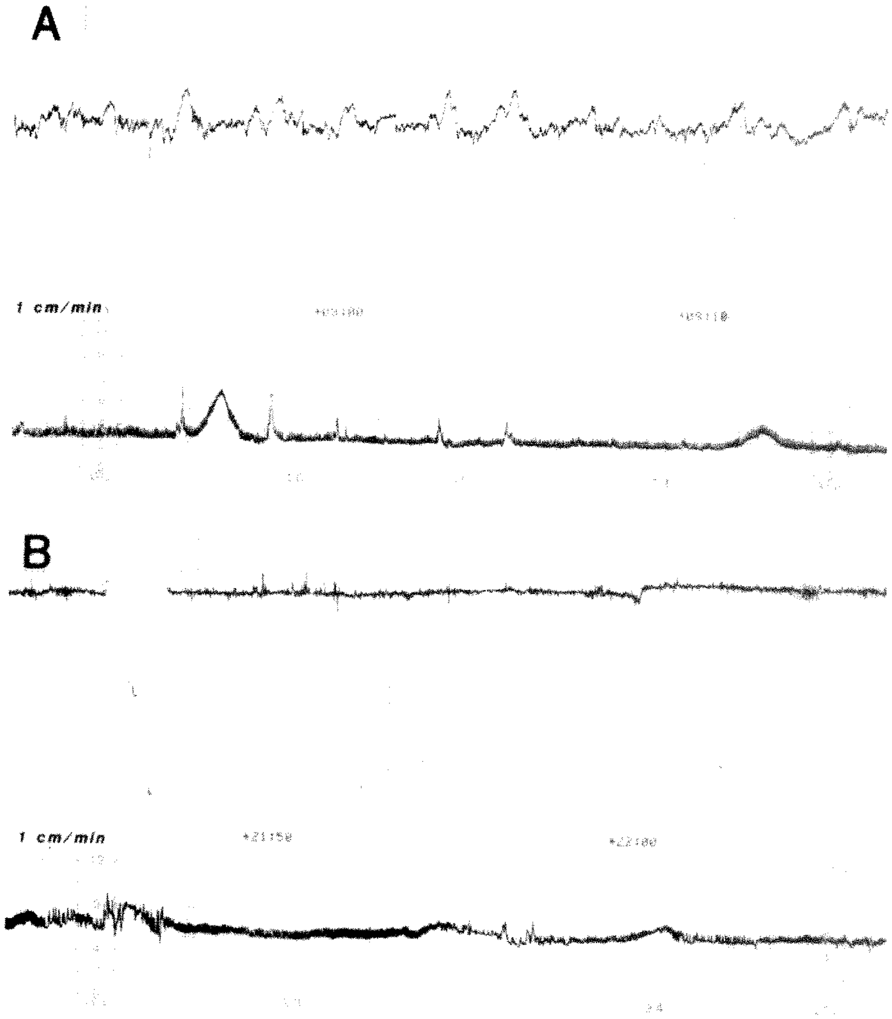

Fig. 2. Representative examples of Doppler ultrasound recordings of the FHR in patient 2, at admission (A) and 12 h later (B). Paper speed 1 cm/min.

acquired hypoxic encephalopathy has been reported by Fricker *et al.* (1983), but the FHR showed more variability and the child survived, although it was severely handicapped.

What all these cases have in common is a fixed FHR with a relatively high frequency of 150–170 beats/min and a lack of decelerations. In the newborn infant, Kero *et al.* (1978) showed that lack of heart rate variability may also be an indicator for brain death. Furthermore, the blood-gas values are normal, there are no signs of infection, and echoscopic examination reveals no abnormalities. A fixed heart rate can also be seen during fetal behavioural state 1F (Nijhuis 1986) after the use of drugs (e.g. diazepam, pethidine) by the mother and in some cases of anencephaly (de Haan *et al.* 1971), and these causes should therefore be excluded.

These examples give evidence that there may be a wide scatter of pathology which is caused by periods of hypoxia of unknown duration and at various times in the last trimester of pregnancy. The phenomenon of fetal brain death might therefore have the same aetiology as the more frequent cases of 'unexpected sudden fetal death'; the difference might be that in these cases the hypoxia had probably lasted rather longer. In conclusion, if a markedly fixed FHR without decelerations is discovered, a diagnosis of brain death should be considered after exclusion of the possibilities mentioned above. If fetal brain death is then suspected and it is not possible to take a blood sample from the fetal scalp, it is useful to consider taking a blood sample directly from the umbilical cord (cordocentesis) (Nicolaides *et al.* 1986). In this way fetal distress can be excluded and unnecessary operative intervention can be avoided.

References

Adams, R. D., Prod'hom, L. S. & Rabinowicz, Th. (1977) Intrauterine brain death. *Acta Neuropathol* **40,** 41-49.

de Haan, J., van Bemmel, J. H. & Stolte, L. A. M. (1971) Quantitative evaluation of the fixed heart rate during pregnancy and labor. *Eur J Obstet Gynecol Reprod Biol* **3,** 103-107.

Fricker, H. S., Sauter, M. & Buchs, B. (1983) Antepartale hypoxische Hirnschädigung (antepartale CTG- und postpartale CT-Veränderungen). *Z Geburtshilfe Perinatol* **187,** 50-53.

Kero, P., Antila, K., Ylitalo, V. & Välimäki, I. (1978) Decreased heart rate variation in decerebration syndrome: quantitative clinical criterion of brain death? *Pediatrics* **62,** 307-311.

Nicolaides, K. H., Soothill, P. W., Rodeck, C. H. & Campbell, S. (1986) Ultrasound-guided sampling of umbilical cord and placental blood to assess fetal wellbeing. *Lancet* **i,** 1065-1067.

Nijhuis, J. G. (1986) Behavioural states: concomitants, clinical implications and the assessment of the condition of the nervous system. *Eur J Obstet Gynecol Reprod Biol* **21,** 301-308.

van der Moer, P. E., Gerretsen, G. & Visser, G. H. A. (1985) Fixed fetal heart rate pattern after intrauterine accidental decerebration. *Obstet Gynecol* **65,** 125-127.

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SHORT COMMUNICATIONS

Prevalence of human papillomavirus types in the cervices of women before and after laser ablation

M. A. Byrne *Hon. Senior Registrar,* D. Taylor-Robinson *Consultant Microbiologist, Jefferiss Research Wing of the Praed Street Clinic, St Mary's Hospital, Paddington and the Division of Sexually Transmitted Diseases, Clinical Research Centre, Harrow, Middlesex,* C. Wickenden *Research Scientist,* A. D. B. Malcolm *Professor of Biochemistry, Department of Biochemistry, Charing Cross and Westminster Medical School, London W6,* M. C. Anderson *Senior Lecturer in Gynaecological Pathology,* D. V. Coleman *Reader in Cytopathology, Department of Pathology, St Mary's Hospital Medical School, London W2*

In a recent study (Wickenden *et al.* 1987), human papillomavirus (HPV) DNA was detected in 49% of samples from women previously treated by laser ablation for cervical intraepithelial neoplasia (CIN) of grades 2 and 3. All the patients were reported to have normal cervical cytology and a normal colposcopic appearance of the cervix at the time of sampling. More surprising was the finding of HPV type 6 in most of the positive samples. In other studies (Dürst *et al.* 1983; McCance *et al.* 1985) it is HPV types 16 and 18 that have been found frequently in association with the more severe lesions, namely CIN 3 and invasive cancer. However, Wickenden *et al.* (1987) did not have information on the HPV status of the cervix before laser treatment and it was not possible to differentiate between persistence of the virus after ablation and re-infection. In this study, we have determined the viral types in the cervices of women before and after laser treatment.

Patients, methods and results

Seven women with CIN 3 attending the colposcopy clinic at the Samaritan Hospital for Women, London, were studied. As described previously (Wickenden *et al.* 1985), a cervical scrape was taken with an Ayre's spatula for cytological examination and HPV DNA hybridization analysis. Samples were obtained both before and after carbon dioxide laser vaporization of the transformation zone, together with the adjacent few millimetres of normal squamous epithelium.

The results are summarized in Table 1. In the pretreatment samples, HPV type 16 was

Table 1. Prevalence of human papillomavirus (HPV) types before and after laser ablation of cervical intraepithelial neoplasia in seven women

Patient no.	Presence of HPV type						Interval between first and second sampling (months)
	6		16		18		
	Before	After	Before	After	Before	After	
1	–	–	–	–	–	–	5
2	–	+	+	–	–	–	17
3	–	–	+	–	–	–	5
4	–	–	+	–	–	–	5
5	–	–	+	–	–	–	15
6	–	–	+	–	+	–	5
7	–	–	+	–	–	+	17

All samples were negative for HPV 11.

detected in 6 (86%) and HPV type 18 in 1 (14%). Types 6 and 11 were not detected in any of the samples. In the post-treatment samples, HPV type 16 was not detected but types 6 and 18 were found, each in one patient only although these types had not been found in these two patients before treatment. None of the patients had cytological or colposcopical evidence of CIN when they were sampled at the post-treatment examination.

Discussion

In common with other reports (Dürst *et al.* 1983; McCance *et al.* 1985) the results of this study confirm the frequent finding of HPV type 16 in association with untreated CIN 3. They also clearly demonstrate that this particular virus type disappears from the cervical epithelium after laser destruction of the transformation zone. HPV types 6 and 18 were detected after laser treatment in two patients who apparently did not harbour these HPV types before treatment. It would appear, therefore, that re-infection of the healing area by persistent virus spreading from the surrounding epithelium did not occur in these patients although this has been suggested as a possible cause of recurrent neoplasia (Ali *et al.* 1986). The interval between laser treatment and sampling was considerable in both patients and it seems that re-infection from a sexual partner rather than spread was the likely means of acquiring the new virus type.

In the two women who were positive for HPV DNA after laser treatment, no cytological or colposcopical evidence at the time of sampling was found for residual or recurrent CIN. However, our results clearly show that the cervix is still permissive for harbouring HPV. It is possible that the mature, healed squamous epithelium that develops in most cervices after laser treatment does not have the same potential for neoplastic transformation as the pretreatment epithelium of the transformation zone. As a point of interest it is notable that a new transformation zone develops in some women after laser therapy. Clinically this appears as an 'erosion' which becomes white after application of acetic acid and histological examination reveals immature squamous metaplasia. In some patients the cervix may remain in this state for some years and these women could be at increased risk of recurrent neoplasia particularly if they continue to harbour HPV or become re-infected.

The non-invasive technique we used here is particularly appropriate for the identification of women infected by HPV and we are continuing to examine the prevalence of these viruses and the effect of laser treatment in a much larger prospective study. It will be particularly interesting to observe if the patient harbouring HPV type 18 develops further CIN. Any method that allows the identification of the subset of women at risk of recurrent neoplasia will be welcome.

References

Ali, S. W., Evans, A. S. & Monaghan, J. M. (1986) Results of CO_2 laser cylinder vaporization of cervical intraepithelial disease in 1234 patients. An analysis of failures. *Br J Obstet Gynaecol* **93,** 75-78.

Dürst, M., Gissmann, L., Ikenberg, H. & Zur Hausen, H. (1983) A papillomavirus DNA from a cervical carcinoma and its prevalence in cancer biopsy samples from different geographic regions. *Proc Natl Acad Sci* **80,** 3812-3815.

McCance, D. J., Campion, M. J., Clarkson, P. K., Chesters, P. M., Jenkins, D. & Singer, A. (1985) Prevalence of human papillomavirus type 16 DNA sequences in cervical intraepithelial neoplasia and invasive carcinoma of the cervix. *Br J Obstet Gynaecol* **92,** 1101-1105.

Wickenden, C., Malcolm, A. D. B., Steele, A. & Coleman, D. V. (1985) Screening for wart virus infection in normal and abnormal cervices by DNA hybridisation of cervical scrapes. *Lancet* **i,** 65-67.

Wickenden, C., Malcolm, A. D. B., Byrne, M. A., Smith , C., Anderson, M. C. & Coleman, D. V. (1987) Prevalence of HPV DNA and viral copy numbers in cervical scrapes from women with normal and abnormal cervices. *J Pathol* **153,** 127-135.

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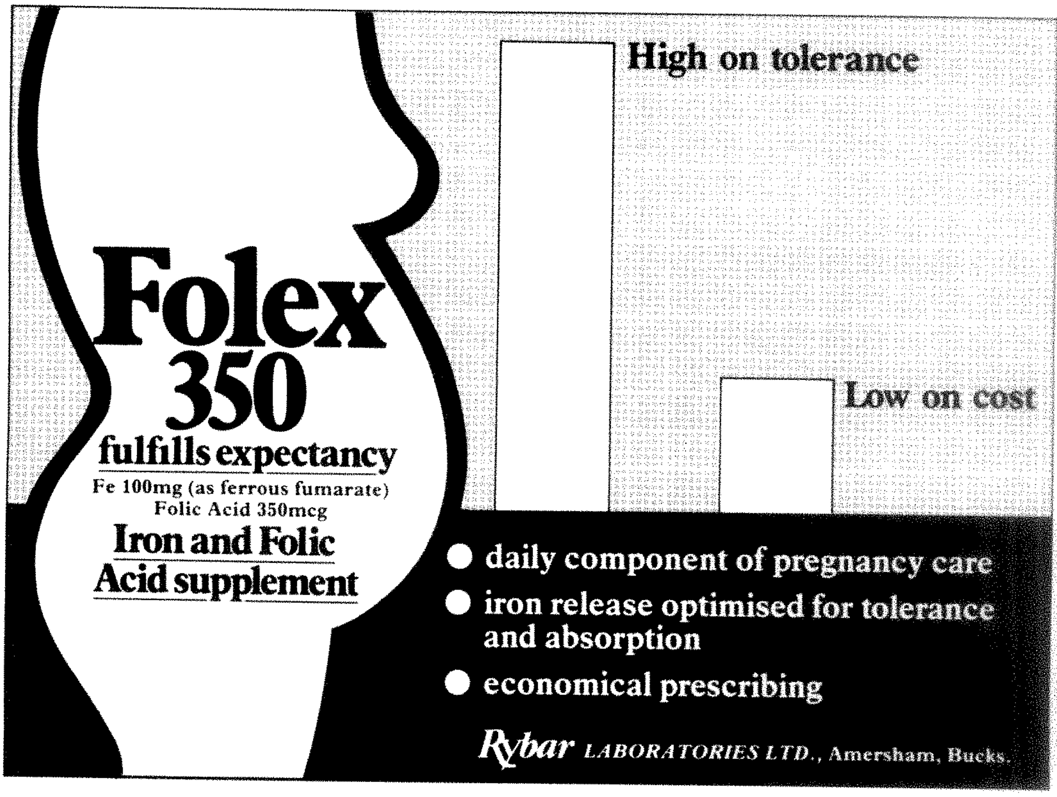
Accepted 30 June 1987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Further details are available from:- **Miss B J Stevens, Postgraduate Education Department, Royal College of Obstetricians and Gynaecologists.**

THE CASE
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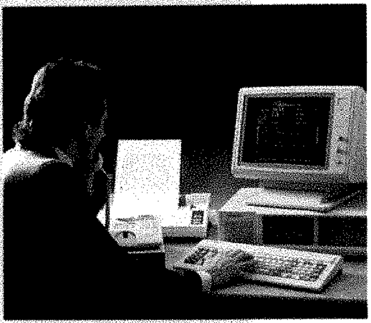

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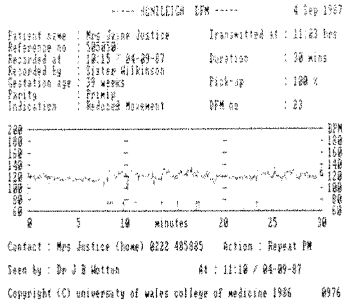

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----- HUNTLEIGH  DFM -----              4 Sep 1987

Patient name    : Mrs Jayne Justice       Transmitted at : 11:03 hrs
Reference no    : 585030
Recorded at     : 10:15 / 04-09-87        Duration       : 30 mins
Recorded by     : Sister Wilkinson
Gestation age   : 39 weeks                Pick-up        : 100 %
Parity          : Primip
Indication      : Reduced Movement        DFM no         : 23

Contact : Mrs Justice (home) 0222 485885    Action : Repeat PM

Seen by : Dr J B Wotton                At : 11:10 / 04-09-87

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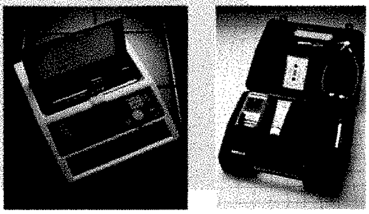
...and transmitted to hospital in 45 seconds for expert interpretation.

. . . AND MORE FROM



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British Journal of Obstetrics and Gynaecology
February 1988, Vol. 95, pp. 203–205

CORRESPONDENCE

Maternal posture in second stage and fetal acid base status

Dear Sir,

Johnstone *et al.* [*Br J Obstet Gynaecol* (1987) **94**, 753–757] determined a 15° tilt by placing a pillow or towels under the right hip; they do not provide evidence first of all that a 15° tilt was consistently achieved by this method and that it adequately supported the patient at 15° in second stage, nor do they provide evidence that during the second stage this position improves placental perfusion in comparison with the dorsal position Kauppila *et al.* (1980) compared the dorsal position with the left lateral (45°) position. In fact the importance of maternal position in first stage may have been underestimated.

In endeavouring to compare the two positions the authors studied two dissimilar groups of patients who were not matched for gestation, parity or risk factors; for example, from Table 1, nine patients in the 'back' group had meconium-stained amniotic fluid compared with four in the '15° tilt' group. No mention is made of when meconium staining was first noted, was it on presentation or did it develop in labour, the amniotic fluid being initially clear. Furthermore 40% of the patients received oxytocin but it is not stated who received it, why, or when it was administered in relation to the first or second stage.

In a study on the second stage it is surprising that the authors did not clearly state their working definition and how they made the diagnosis. The impression from their report is that the onset of the second stage was timed when the patient developed the urge to push. Clinical experience indicates that the patient is not always right in her diagnosis. For the day-to-day management of a busy labour ward such a working diagnosis is in general satisfactory but, I suggest, it is not acceptable in a research setting

Cord artery pH values, as with so many other fetal and neonatal variables, show a wide range of 'normal' values. Two recent studies, using cord artery pH values in normal pregnancies and labours, in which the duration and position of the patient in the second stage were not considered, reported wide ranges of values for infants normal at birth (Yeomans *et al.* 1985; Ingermarsson & Arulkumaran 1986).

Finally the benefits of the left lateral position to patient and fetus during the second stage may outweigh the disadvantages to the midwife more accustomed to delivering patients in the dorsal position.

Desmond P. J. Barton
National Maternity Hospital
Holles Street, Dublin 2
Ireland

References

Johnstone, F D., Aboelmagd, M. S & Harouny, A. K. (1987) Maternal posture in second stage and fetal acid base status *Br J Obstet Gynaecol* **94**, 753-757.

Kauppila, A , Koskinsen, M., Puolakka, J., Tuimala, R & Kuikk, J. (1980) Decreased intervillous and unchanged myometrial blood flow in supine recumbency. *Obstet Gynecol* **55**, 203-205

Ingemarsson, I. & Arulkumaran, S. (1986) Fetal acid-base balance in low-risk patients in labor *Am J Obstet Gynecol* **155**, 66-69

Yeomans, E R., Hauth, J C., Gilstrap, L C. & Strickland, D H. (1985) Umbilical cord pH, $P\text{co}_2$, and bicarbonate following uncomplicated term vaginal deliveries. *Am J Obstet Gynecol* **151**, 798-800.

Authors' reply

Dear Sir,

I appreciate Dr Barton's helpful comments on our paper. The study design, which aimed to test a single intervention in a routine clinical situation, was determined by a combination of scientific and practical considerations. Apart from posture, we did not seek to influence clinical management in any way, and this included the diagnosis of second stage. We also decided against deliberate matching, because to have matched even in three bands for the number of relevant variables would have generated an unworkably large number of cells. Instead, we tried to ensure comparability of groups by random allocation. This turned out to be only moderately successful; differences between groups were small and not statistically significant (except for gestation) but did tend to favour the 'tilt' group. In particular, Dr Barton is correct to highlight meconium staining. The babies in the group with meconium-stained amniotic fluid were more acidotic and included the only profoundly acidotic baby, and although there was no statistically significant difference between the numbers ($\chi^2 = 1{\cdot}25$, $0{\cdot}30>P>0{\cdot}20$) neither were they very equally distributed, to the disadvantage of the 'back' group. In retrospect, I agree that this very important variable should have been matched, together with parity, but I am not convinced that the design should have called for matching of other variables. All women given oxytocin started this in the first stage of labour, and it was given because of failure to establish or progress in labour.

We have no evidence that a 15° tilt was consistently achieved, and it is hard to think what sort of evidence Dr Barton has in mind. Nor should position be thought of as static. Women do move and adjust position to some extent even in second stage. Indeed our impression was that the amount of movement—towards the lateral and back to the dorsal position—was greater in the 'tilt' group, and this itself may be an important difference between the two treatments.

Finally, we are well aware of the wide range of 'normal' pH values in this context, and significantly there was no suggestion of any difference in clinical condition of the babies. Despite these caveats, however, we believe our cautious conclusions are justified. Encouraging women to lie in the flat dorsal position on a narrow obstetric table for second stage is a medical intervention, albeit with very definite benefit in terms of ease of supervision, and could possibly in some cases result in iatrogenic morbidity, as I think Dr Barton agrees.

Frank D. Johnstone
Senior Lecturer
Department of Obstetrics and Gynaecology
37 Chalmers Street
Edinburgh EH3 9EW

In defence of the obstetrician

Dear Sir,

In his commentary 'In defence of the obstetrician' [*Br J Obstet Gynaecol* (1987) **94**, 833–835] Mr Macdonald speaks of modern technological delivery units as providing 'the best chance of a live and healthy mother and baby'.

This may be so in the small number of women who have a risk factor which requires obstetric intervention, but there is not a shred of evidence that normal, healthy, well-fed women benefit from having their babies in a high-tech unit. All the research points to perinatal mortality and morbidity being strongly associated with low socio-economic factors among women and their families. The 'Black Report' (1980) and the recent Health Education Council Report (1987) make this point clearly and cogently, and it has never been refuted.

Comparing home birth today with domiciliary obstetrics before the establishment of the welfare state is ludicrous. Housing conditions, good nutrition, running hot water, hygiene and personal health are immeasurably improved. Even more important, women are not now worn out by constant childbearing and unremitting household chores. They are fit, healthy, and on the whole space their families intelligently. Tew (1984, 1985*a*, *b*) and later Campbell & Macfarlane (1987) have shown conclusively that planned home birth in a low-risk pregnancy has a better perinatal outcome than an equally low-risk pregnancy delivered in an obstetric unit. Childbirth, except in a few unfortunate cases, is not a medical, but a normal physiological event, and should be left to women and midwives. When and if things go wrong, as is bound to happen in a small minority of cases, then the skill and expertise of the consultant obstetrician is gratefully accepted, but birth should be regarded as normal unless something unforeseen develops. Women allowed to labour peacefully, in their own time, with known and trusted attendants, and in safe familiar surroundings, are far less likely to need obstetric intervention, and the home provides just such an environment.

It is not surprising that Mr Macdonald does not approve of the WHO report *Having a Baby in Europe* and the RCM statement detailing the future training needs of midwives. These two documents spell out a message he and others with his attitudes do not want to hear; that what is needed is a substantial shift in the balance of power and control over childbirth away from the medical model and pathology, back to women, midwives and normality. The cosmetic changes at the Clarendon Wing in Leeds do not address these issues at all.

By treating birth as a risky medical procedure, obstetricians create an aura of anxiety in the labouring woman, which undermines her confidence in her own body's ability to perform a function it is well designed for. Women will put up with all kinds of pain, difficulties and uncomfortable procedures, so long as they feel in control of the decision-making process and are fully involved at every step. Our recent publication (Kitzinger 1987) shows quite clearly that what was important to women was not whether they did or did not have pain relief, but whether *they* had decided that they needed it, and it was provided when asked for, and not pressed upon them when they did not want it.

Mr Macdonald should remember that health is defined far more widely than in the technically physical sense. A healthy mother is emotionally satisfied after the birth, ready to start on a vital new relationship with an alert and responsive, mentally and physically healthy baby. Childbirth is a life event of the most crucial long-term emotional consequence to a woman and her family, and obstetricians who persist in treating it as simply a technical exercise are doing future society immeasurable harm.

Hanna Corbishley
National Secretary
The National Childbirth Trust
9 Queensborough Terrace
London W2 3TB

References

The Black Report (1980) *Inequalities in Health,* DHSS, London.

Campbell, R & Macfarlane, A. (1987) Where to be Born. *National Perinatal Epidemiology Unit Publication,* Oxford

Health Education Council Report (1987) *The Health Divide,* Health Education Council, London.

Kitzinger, S (1987) *Some Women's Experiences of Epidurals* National Childbirth Trust, London

Tew, M. (1984) The myth of hospital safety. *AIMS Journal.* Spring 1984.

Tew, M. (1985*a*) Place of birth and perinatal mortality *J R Coll Gen Pract* **35,** 390-394.

Tew, M. (1985*b*) We have the Technology. *Nursing Times & Mirror,* 20th November, 22-24.

Authors' reply

Dear Sir,

Thank you for giving me the opportunity to respond. Yes indeed it is the socially deprived woman who is more at risk of obstetric complications such as anaemia, premature labour or growth retardation, and requires more help, but if the National Childbirth Trust can predict which healthy woman will not develop a late unexplained intrauterine death, deep transverse arrest in a first labour, or postpartum haemorrhage with any delivery we would love to know how. The nub of our difference is that the professional obstetricians say it is not just 'a small number of women with a risk factor' who have problems, but a substantial majority who have sufficient risk of obstetric complications to justify delivery where there are additional facilities if required.

Certainly home conditions are much better than they were and I have, of course, read the statistical papers by Marjorie Tew and Rona Campbell but do not feel that they carry sufficient scientific weight to persuade a major change in NHS practice from hospital to home delivery. 'The ingenuity of Tew in manipulating published data' (Alberman 1986) does not help their case. As the original article said, 'Let those who wish, arrange a new study of home delivery' in present circumstances, in order to prove their case in practice. Most of our deliveries are undertaken by the midwives anyway; it is not a question of obstetricians seeking 'power and control' but of health, safety and satisfied customers.

Obstetricians do not treat childbirth as 'simply a technical exercise' and to accuse them of 'doing future society immeasurable harm' represents the kind of extraordinary intolerance which prompted the article in the first place.

May I invite Ms Corbishley to visit the Clarendon Wing and see a caring service for herself She might even find some of her prejudices soften a little.

R. R. Macdonald
Consultant Gynaecologist
Clarendon Wing
The General Infirmary
Belmont Grove, Leeds LS2 9NS

Reference

Alberman, A. (1986) The place of birth. *Br J Obstet Gynaecol* **93,** 657-658.

British Journal of Obstetrics and Gynaecology
February 1988, Vol. 95, pp. 206–208

BOOK REVIEWS

Clinics in Obstetrics and Gynaecology Vol. 13/No. 3 The Human Placenta edited by Tim Chard. W. B. Saunders Co., London, Philadelphia, 1986, 421–663 pages with figures and tables, £13.50

Is the proper study of the placenta the health of the fetus? In some ways it is, but the placenta is independent and worthy of individual study. Does it not have respiratory and metabolic requirements, as well as a unique structure and function? Although its relevance to maternal adaptation in pregnancy is not fully understood, and the factors which control its growth and function still need considerable investigation, much is known. This volume of *Clinics* reviews many recent advances, concentrating on pathology rather than physiology but it starts with an excellent chapter on the light and electron microscopic appearances of the healthy placenta, with illustrations so informative that they require an extensive key section to themselves. Transfer functions are mentioned but not discussed specifically, they are inferred more from the success in discovering disorders by biophysical monitoring which is discussed critically. Endocrine function early and late in pregnancy is described from the cellular to the maternal level. The consensus is that biophysical tests are useful in assessing fetal health, and that the endocrine investigations complement them. A succinct and informative chapter on the pathology of the placenta by Fox contains a section on immunology. There is also a full chapter on the immunology of the placenta by Redman with an extensive glossary which is very helpful for the uninitiated. Together these chapters illuminate this most arcane of topics in obstetrics, but they do not pretend to explain everything. The value of placental tissue in antenatal diagnosis necessarily receives a chapter, as does haemorrhage from the placental site. Not surprisingly placental proteins occupy much of the space in the volume. This is because they are relevant not only to obstetrics but to oncology. Their significance in oncology is explained both practically and theoretically. Indeed the whole volume is a satisfactory amalgam of theory and practice. It brings together a lot of information (some so up to date it is still 'in press') which is not readily found in any one place. This is a clinically valuable book of definite views which is readable and informative, as would be expected from a group of authors actively investigating the field which they discuss.

I. R. McFadyen

The Foetus as Transplant Donor: Scientific, Social and Ethical Perspectives by Peter McCullagh. John Wiley & Sons, Chichester, New York, 1987, 215 pages with figures and tables, £25.00

This book is a comprehensive analysis of a subject with strong scientific, social and ethical overtones, as its subtitle suggests. The author ranges widely over the issues raised and the four parts of the book cover the background (e.g. fetal tissue transplantation and abortion); specific examples of fetal tissue transplantation; the status of the human fetus; and 'wider issues' which debates issues relating to the donor, the recipient, the scientist, and society as a whole

First impression suggests that the subject is too narrow to be of general interest but this does the book and the author a great disservice. Although the specific issue of fetal tissue transplantation may currently be of relatively minor practical importance in the context of global health issues, it raises such important questions that it must be addressed. This is not only for its own sake but as an example of how scientists and clinicians should approach issues at the forefront of technology and the front line of ethics with a framework which allows consistency of argument, and is both morally and scientifically sound. As the author states 'any discussion of the ethical aspects of a medical procedure will be unproductive, if not entirely misleading, unless it is based on a clear understanding of the verifiable scientific findings which underpin the procedure'.

Early in the book the author talks about the community's requirement of its scientists as being determined by what 'can be done' and what 'needs to be done'. My marginal note asks 'Where is the "What ought to be done?" ' I am glad to say, however, that he deals with this 'technological imperative' later and in so doing provides food for thought and cause for caution.

Everyone whose practice involves them with these 'front line' issues should, in the words of the Prayer Book, 'read, mark, learn and inwardly digest' this book. They will not necessarily agree with it in its entirety but it will act as a catalyst for personal thought and action. It is all too easy to be critical of such a work, and I fear that it is not going to be widely read. A distillation of its contents in a series of articles in the 'popular' medical press would be valuable. If I were to encapsulate the whole in one sentence, it would be that quoted by the author as a chapter heading by Guttentag, 'The moral history of mankind is more important than the scientific'. We forget that at our peril.

Gordon M. Stirrat

Obstetrics: Normal and Problem Pregnancies edited by Steven G. Gabbe, Jennifer R. Niebyl & Joe Leigh Simpson. Churchill Livingstone, Edinburgh, 1986, 1148 pages with figures and tables, £60.00

For the past couple of months I have been dipping into *Obstetrics: Normal and Problem Pregnancies*. This 1100-page American obstetrics textbook aims to provide 'a reference source for the general practice of obstetrics' and 'the necessary base of information for those in fellowship programmes in maternal-fetal medicine'. It is a multiple author work with 42 American contributors and is divided into three main sections dealing with anatomy and physiology of pregnancy, normal care and complicated pregnancy care. There are supplementary sections on pregnancy termination and legal and ethical issues.

The first impression on opening this book is of the very clear type which does not tire the eye. The editors have allowed liberal use of illustrations, mostly line drawings. The 26 drawings illustrating pelvic anatomy are particularly clear and helpful and I was impressed by the use of diagrams in the exposition of physiological mechanisms throughout the book. There is no doubt that obstetricians now have to maintain a relatively sophisticated understanding of a much wider field than their predecessors. This book addresses that need and provides clear chapters on genetics and prenatal diagnosis, teratology and birth defects, drugs in pregnancy and lactation, and extensive chapters on antenatal and intrapartum fetal assessment, but I was disappointed to find no account of current thoughts on the aetiology of pre-eclampsia. The 109-page section on medical complications (excluding hypertension) is comprehensive and could stand as a small textbook on its own but there is the usual problem with American texts that drug names are often different from those in British practice. It is a recurring problem with the use of American textbooks in British-influenced obstetrics that some sections are inappropriate because of differences in clinical practice. Obvious examples are in the management of eclampsia and the preference for outpatient dilatation and evacuation for mid-trimester abortion.

The understandable concern of American obstetricians with litigation is perhaps the basis for the many statements found throughout the book declaring recommendations for particular actions in specific circumstances. I can envisage these guidelines being extremely useful for obstetricians wishing to ensure that their actions can be defended in court. The concern with litigation is further emphasized by a fascinating chapter on the legal issues in American practice. The issues discussed include a three million dollar 'wrongful life' suit concerning a child born with Tay Sachs disease where the prenatal screening had given a false negative result; and a 'forced caesarean section' suit in a 157 kg 'hypertensive, angry and uncooperative' woman with no prenatal care, with a 2 cm dilated cervix, meconium staining and an ominous FHR trace who demanded to leave the hospital against medical advice. Difficult medico-legal issues indeed.

If this book had been written in the context of British obstetric practice I could warmly recommend it. As it stands it is still a very worthwhile publication which is reasonably priced at £60.00.

David H. Barlow

Books received some of which may be reviewed at a later date

Prematurity edited by Victor Y. H. Yu & E. Carl Wood. Churchill Livingstone, Edinburgh, 1987, 292 pages with figures and tables, £30.00

Hemostatic Disorders of the Pregnant Woman and Newborn Infant by William E. Hathaway & John Bonnar. John Wiley & Sons, Chichester, 1987, 223 pages with figures and tables, £39.50

Gynecologic Cancer: Diagnostic and Treatment Strategies edited by F. N. Rutledge, R. A. Freedman & D. M. Gershenson. University of Texas Press, Austin, 1987, 500 pages with figures and tables, $65.00

The Infertile Couple edited by R. J. Pepperell, Bryan Hudson & Carl Wood. Churchill Livingstone, Edinburgh, 1987, 391 pages with figures and tables, £24.95

Fertility and Family Planning in the Third World: A Case Study of Papua New Guinea by William K. A. Agyei. Croom Helm Ltd, Beckenham, 1987, 208 pages with figures and tables, £19.95

Missed Beginnings: Death Before Life has been Established by June Jolly. Austen Cornish Publishers Ltd, London, in association with The Lisa Sainsbury Foundation. Available from The Lisa Sainsbury Foundation, 8–10 Crown Hill, Croydon, Surrey CR0 1RY, £3.50 (incl. p. & p.)

Barrier Contraceptives and Spermicides: their Role in Family Planning Care World Health Organization, Geneva, 1987, 80 pages with figures and tables, Sw.fr. 15

Sickle-Cell Anemia and Thalassemia. A Primer for Health Care Professionals published by the Canadian Sickle Cell Society, PO Box 13156, Station A, St John's, Newfoundland, Canada, A1B 4AA, £5.00

Critical Care Obstetrics edited by S. L. Clark, J. P. Phelan & D. B. Cotton. Medical Economics Books, Oradell, NJ, USA, 508 pages with figures and tables, $52.95

Proceedings and Symposia

International Strategies for the Eradication of Carcinoma of the Cervix in Developing Areas (Proceedings of the International Working Party Meeting in India 1987) edited by R. F. Mould & Arabinda Bose. Adam Hilger, Bristol, 1987, 293 pages with figures and tables, £50.00

Ovarian Cancer—The Way Ahead (Proceedings of the Seventeenth Study Group of the Royal College of Obstetricians and Gynaecologists in conjunction with The Helene Harris Memorial Trust) edited by F. Sharp & W. P. Soutter. John Wiley & Sons, Chichester, 1987, 481 pages with figures and tables, £39.50

Erratum

Br J Obstet Gynaecol **94**, 1011–1013, 1089–1093

Commentary. Colposcopy: who, when, where and by whom? P. WALKER & A. SINGER

Treatment of cervical intraepithelial neoplasia (CIN) by radical electrocoagulation diathermy: 5 years' experience J. A. GILES, P. G. WALKER & P. A. F. CHALK

We have been informed that the quotation

> 'nearly 70% of patients referred for colposcopy because of a cervical smear which showed simply mild atypia were found on biopsy to have CIN 3'

which was cited in these two papers should have read 'were found on biopsy to have CIN 2 or CIN 3'.

Directions to contributors

All papers should be sent to The Editor *British Journal of Obstetrics and Gynaecology*, 27 Sussex Place, Regent's Park, London NW1 4RG. Papers received are assumed to have been submitted exclusively to the *British Journal of Obstetrics and Gynaecology* and *all* authors must give signed consent to publication in a letter sent with the manuscript. The Editor will decide on the time of publication and retains the usual right to modify the style and length of a contribution, major changes will be agreed with the author(s).

Presentation of manuscripts

Two copies of the manuscript and illustrations should be sent. Manuscripts should be typed double spaced on one side of the paper, with wide margins. The names of author(s) and their appointment(s) and addresses at the time of preparation of the manuscript should be given. Authors are advised to keep a copy of all manuscripts, as no responsibility can be accepted for loss.

Reports of original work should usually be arranged in the conventional order of summary, introduction, methods, results, discussion, acknowledgments and references, with suitable headings for each part. Two further sub-divisions, with appropriately less significant headings, can be used, the third order heading runs on with text at a paragraph opening. Results may be presented in the text, in tables and/or figures, but the text should, in general, comment on rather than repeat information in tables. The summary should contain a factual account of the methods and results in not more than 150 words, rather than a description of the subject of the paper and the opinions of the author(s).

Case reports and short communications do not require a summary or introduction. Short communications should not exceed 600 words and contain no more than one table or figure.

Tables and figures

Tables and figures should be separate from the text, with their positions indicated in the text margin. Both are numbered with arabic numerals. Colour illustrations are allowable only in special circumstances and the author will be expected to meet the cost of reproduction.

Figures should be marked on the back (light in pencil) with the name(s) of the author(s), the figure number, and the top indicated. Each should have a descriptive legend typed on a sheet separate from the figure. Photographs should be unmounted glossy bromide prints of good contrast.

Figures consist of all material which cannot be set in type, such as photographs, line drawings, etc. Tables are not included in this classification and should not be submitted as photographs. Original X-ray films should not be sent—glossy prints must be submitted.

Line drawings should be on white board, arranged to conserve space, and should allow for reduction to 65 mm (single column) or 134 mm (double column).

Typewritten lettering should not be used on illustrations and explanations should appear in the legend not on the figure itself.

The identity of patients in illustrations should be concealed by masking the face or eyes, or written permission for publication from the patient or the parent or guardian must be supplied.

Units and abbreviations

Measurements should be expressed in SI units with the exception of haemoglobin (g/dl) and blood pressure (mmHg). If the original observations were recorded in other units this should be stated, together with the appropriate conversion factors. Standard abbreviations, without punctuation, are used. *Units, Symbols and Abbreviations* (1977) published by the Royal Society of Medicine provides a useful guide. Abbreviations are used sparingly and only if a lengthy name or expression is repeated frequently throughout the manuscript. Words must appear in full on first appearance in both summary and text, followed by the abbreviation in parenthesis.

Drugs are described by their official names but trade names should be indicated in brackets the first time a drug is quoted in the main text.

Statistics

Authors should describe clearly the design of their investigation and the source of the data. All statistical methods should be specified so that it is clear which was used where. Papers omitting this information may be returned without review. The basic principle to follow is to supply sufficient information about the design and methods of analysis to allow the research to be repeated by someone else.

Some points of detail to note are

(1) It is not acceptable to present the results of a statistical analysis solely by a *P* value—actual results such as means or proportions should always be given, along with the test statistic.
(2) The use of confidence intervals is encouraged.
(3) The symbol ± should not be used when presenting SE or SD. Presentation such as 'the mean was 14.2 (SD 3.2) mg' is preferred.
(4) When paired comparisons are made it is desirable to indicate the variability of within-pair differences.
(5) Unusual methods of analysis should be described and/or referenced.

Authors are referred to the general statistical guidelines of Altman *et al* (1983) for advice about the presentation and interpretation of the statistical aspects of their research.

Altman, D. G., Gore, S. M., Gardner, M. J. & Pocock, S. J. (1983) Statistical guidelines for contributors to medical journals. *Br Med J* **286**, 1489–1493.

Human experiments

Manuscripts should contain a statement that the work was approved by the ethics committee of the institution in which it was done and that subjects gave informed consent to the work. The editors reserve the right to reject papers if they consider the ethical justification to be questionable.

References

In the text, use the name of the author(s) followed by their date of publication, where there are two authors use the form Smith & Brown 1972, where there are more than two authors use Robinson *et al* 1979.

Arrange the list of authors quoted at the end of the text in alphabetical order set out as follows.

Name(s) and initials of all author(s), year of publication (in brackets), title of the article, name of the journal (abbreviated according to *Index Medicus*), volume number, first and last page numbers. In the case of books the order is: Name(s) and initials of author(s), year of publication (in brackets), full title, edition, publisher and place of publisher, page numbers. Where appropriate, the chapter title and the names of the editors should be given.

References to 'personal communications' and 'unpublished work' may be quoted in the text but should not be included in the references. Examples of the style to be used are given below.

Trudinger, B. J., Lewis, P. J. & Petit, B. (1979) Fetal breathing in intrauterine growth retardation. *Br J Obstet Gynaecol* **86**, 432–436.

Hytten, F. E. & Leitch, I. (1971) *The Physiology of Human Pregnancy* 2nd edn, Blackwell Scientific Publications, Oxford, p. 26.

Proofs and offprints

Manuscripts should specify the name and address of the author to whom correspondence and page proofs should be sent. Only essential corrections can be accepted, more extensive alterations, which may delay publication, will be charged to the author. Fifty offprints of each paper are supplied free, but additional copies may be ordered on the printed sheet sent with the proofs.

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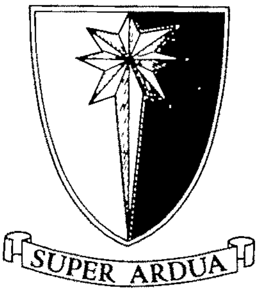
British Journal of Obstetrics and Gynaecology

Edited by Frank E. Hytten



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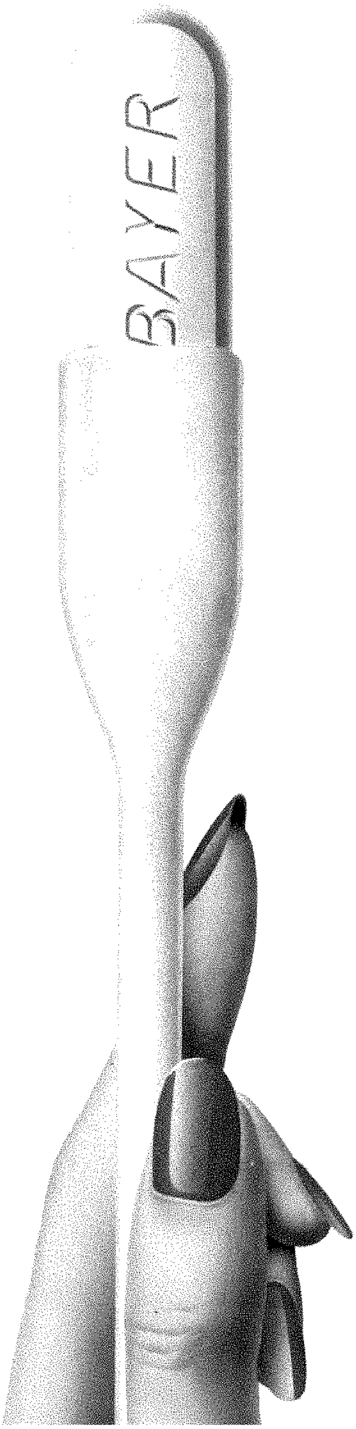

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PRESCRIBING INFORMATION Presentation *Canesten 1* is available as a single vaginal tablet containing 500 mg Clotrimazole BP. **Indications** For the treatment of candidal vaginitis. **Dosage and Administration** *Adults* The single tablet should be inserted preferably at night. *Children* As this product is used with an applicator, paediatric usage is not recommended. **Contra-indications** None known. **Side Effects** Rarely patients may experience local mild burning or irritation immediately after inserting the tablet. **Use in Pregnancy** In animal studies clotrimazole has not been associated with teratogenic effects but following oral administration of high doses to rats there was evidence of foetotoxicity. The relevance of these effects to topical application in humans is not known. However, clotrimazole has been used in pregnant patients for over a decade without attributable adverse effects. It is therefore recommended that clotrimazole should be used in pregnancy only when considered necessary by the clinician. If used during pregnancy extra care should be taken when using the applicator to prevent the possibility of mechanical trauma. **Accidental Oral Ingestion** In the event, routine measures such as gastric lavage should be performed as soon as possible after ingestion. **Pharmaceutical Precautions** No special storage requirements. **Legal Category** POM **Basic NHS Price** £2.58 per vaginal tablet with applicator. **Product Licence Number** PL 0010/0083.

Reference 1. Ritter, W., Pharmacokinetic fundamentals of vaginal treatment with clotrimazole. *Am. J. Obstet. Gynecol.* 1985; 152(7)(Part 2): 945-7.

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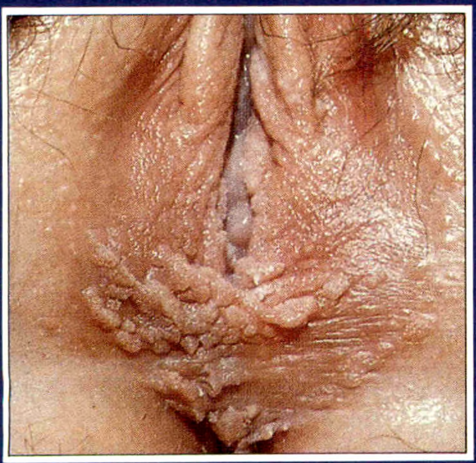

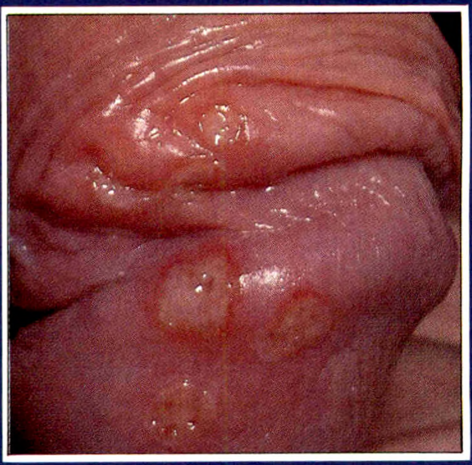

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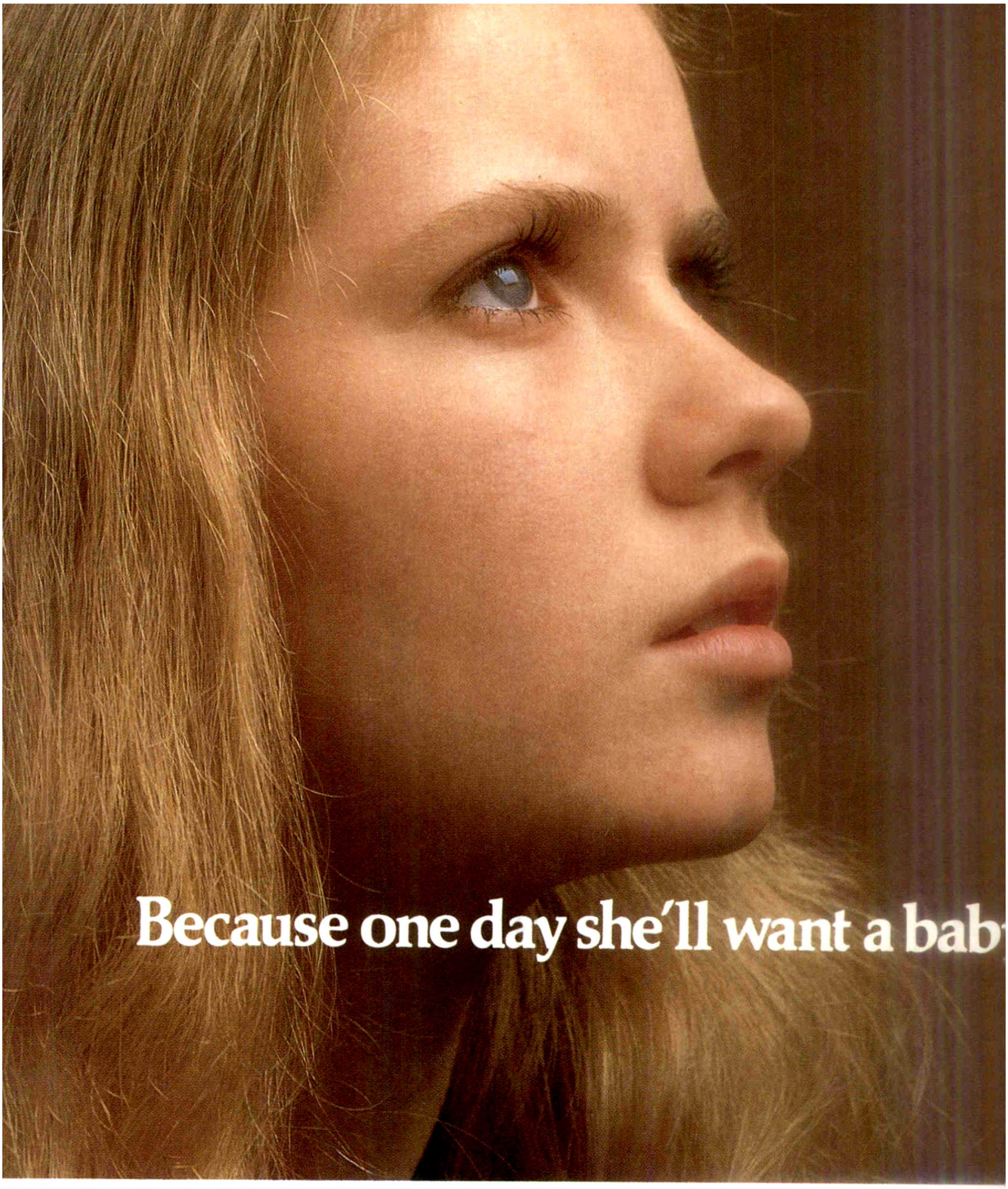
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age One pessary 3 hours before surgery. Allow pessary to warm to
n temperature in unopened foil sachet before use. **Contra-**
cation Hypersensitivity to prostaglandins. **Precautions** Use with
:ion in patients with obstructive airway disease, cardiovascular
fficiency, elevated intra-ocular pressure, cervicitis or vaginitis.
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:xia. **Presentation** Pessary containing 1mg gemeprost in carton of
iit dose foil sachets. **PL No.** 0012/0149. **Basic NHS Cost** (April
5) £82.50 per box. **References:** 1. Harlap,S. *et al.*, *N.Eng.J.Med.*,
9, **301,** 677. 2. Richardson,J.A. & Dixon,G., *Brit.Med.J.*, 1976, **1,**
3. 3. Chen.J.K. & Elder,M.G., *Obstet.Gynecol.*, 1983, **62,** 339.
hristensen,N.J., Bygdeman,M. & Gréen,K., *Contraception*, 1983,
l), 51. Cervagem is a trade mark. Further information is available
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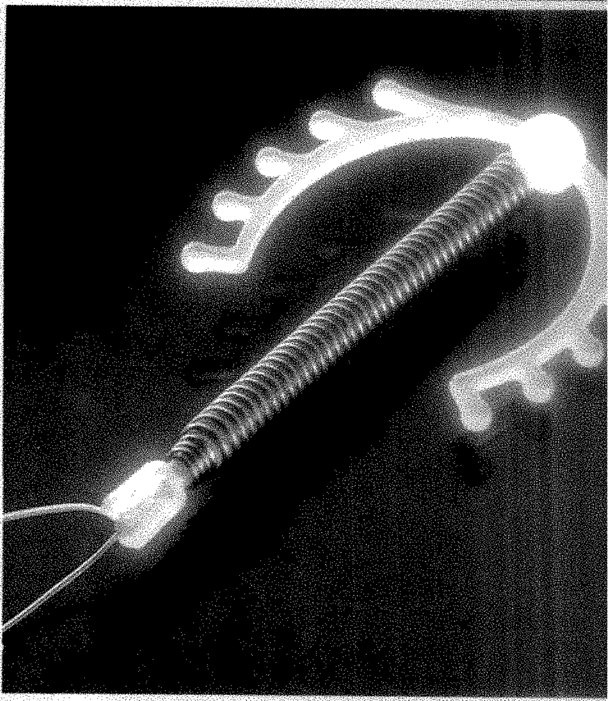

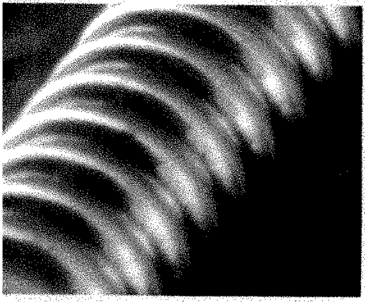

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)ublin, June 1983 pp 129-138

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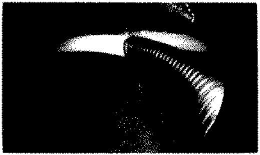
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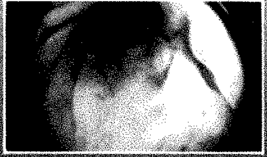
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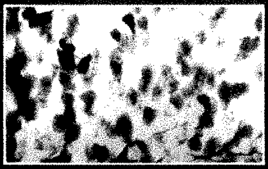
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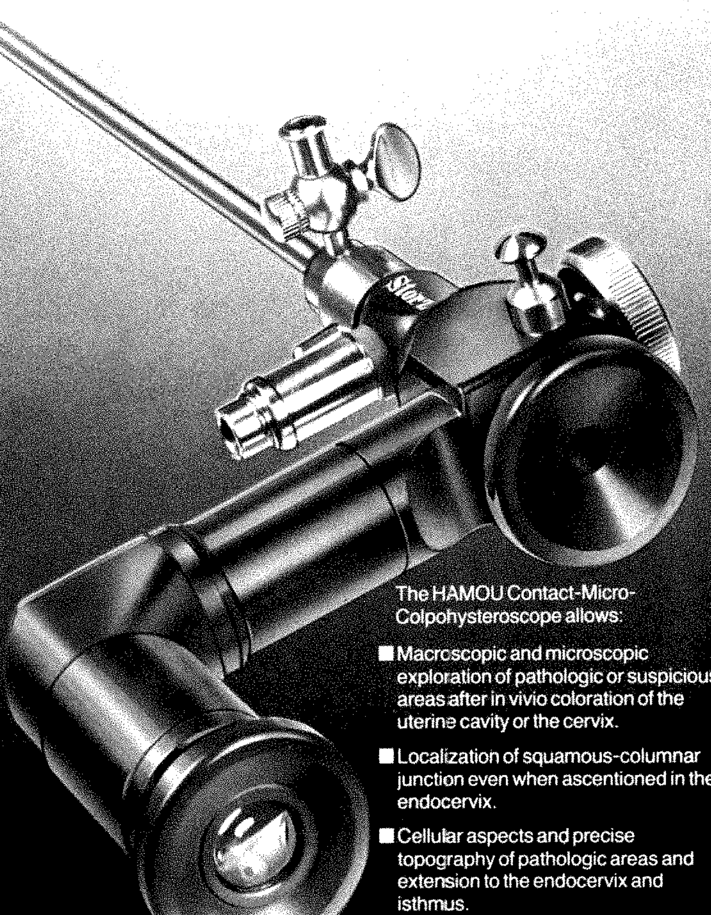

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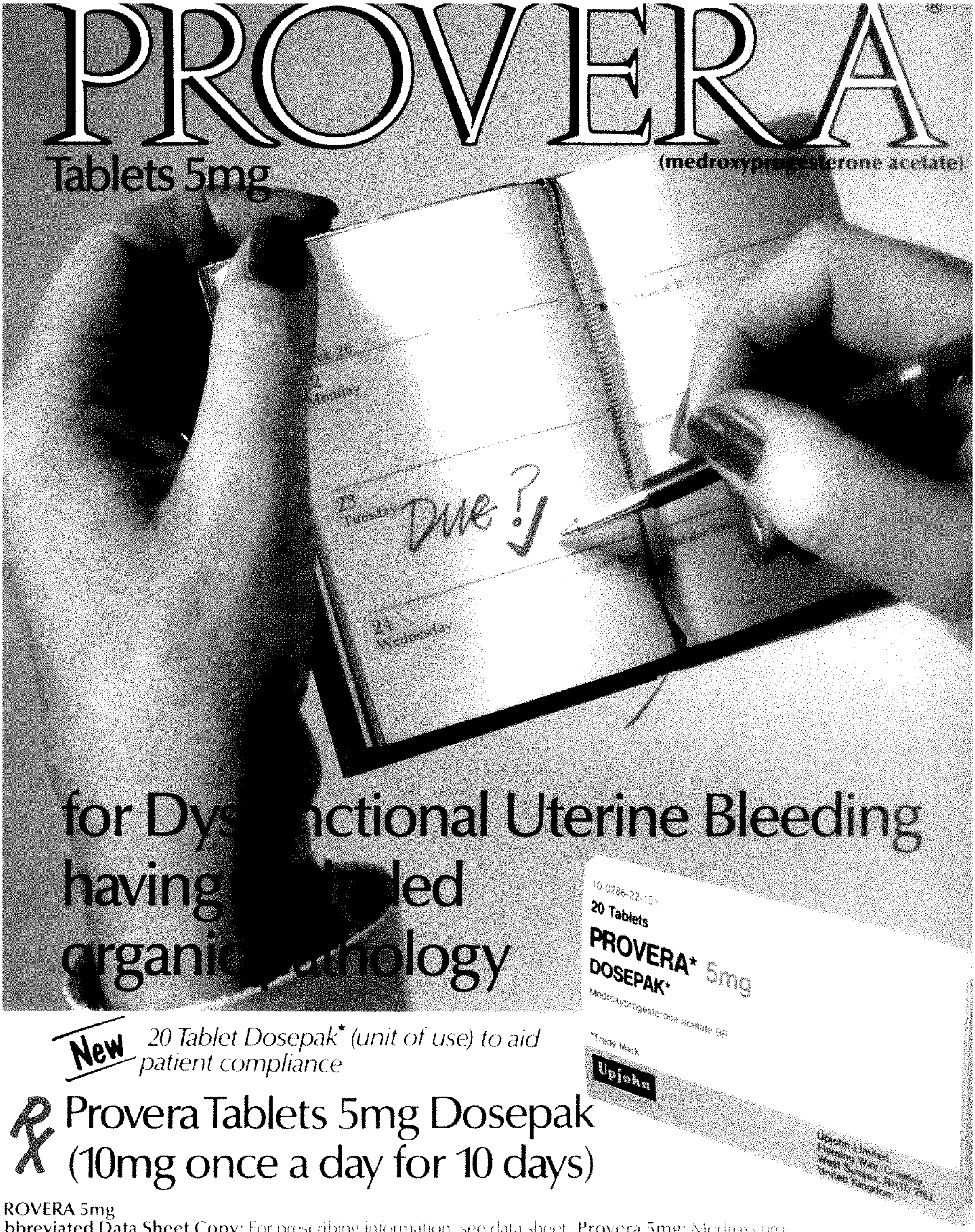

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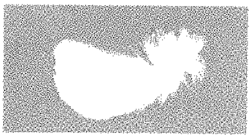

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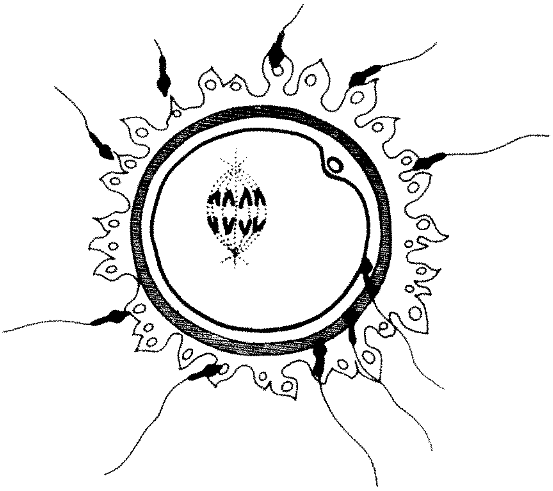

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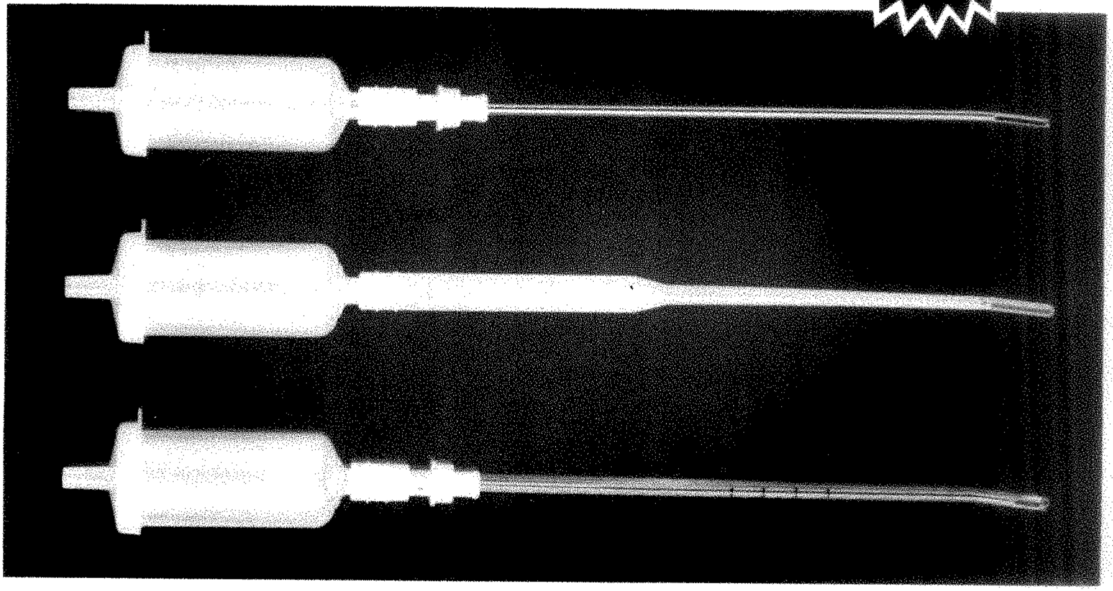

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COMMENTARY

Diseases of animals transmissible to man (zoonoses)

The publication in this issue of the Journal of a case of concomitant infection with ovine chlamydia and 'Q' fever in pregnancy underlines the continuing need for clinicians to be aware of the possibility that infections in their patients may arise from contacts with animals or their products.

Precise statistics on the occurrence of diseases transmissible to man are not readily available but undoubtedly they are responsible for a significant number of human deaths and illnesses. Throughout the world there are over 150 zoonoses caused by bacteria, viruses, protozoa and helminth organisms. Notable among these are the agents of anthrax, brucellosis, salmonellosis, Lassa fever, toxoplasmosis and yellow fever. Apart from causing serious morbidity in man, zoonotic infections undermine animal health and productivity, reducing the production of meat, milk, eggs and wool, and in developing countries diminish the work output of draught animals. Socio-economic losses from zoonoses are also difficult to quantify but the consequential effects arising from these infections can be significant, resulting in the loss of earnings, clinical complications and interference with family life. In addition to the clinical effects, the presence of these infections in a community requires the provision of health services including hospital and laboratory facilities (World Health Organization 1982).

Even though precise figures are not available, studies in the Americas have shown, for example, that about 175 000 persons annually undergo post-exposure treatment for rabies alone. In the 5-year period 1972–1976, in the European area of WHO, 82 000 cases of rabies were diagnosed in animals, 621 deaths occurred in man and more than one million people received post-exposure treatment. Every year throughout the world over 15 000 people die from rabies (World Health Organization 1982). From these figures it is clear that in order to control rabies alone, the strict regulations governing the importation of mammals into the UK are well justified.

In recent years food-borne zoonoses have become increasingly prevalent in many countries. Partly, this is due to the increase in international and national trade in live animals, in animal products and in feedstuffs, all of which facilitate the spread of infection. Also, intensified animal production favours the proliferation of infectious diseases. Environmental changes such as deforestation, immigration, creation of artificial lakes and urbanization may have a marked effect on the ecology of the area. Irrigation systems have been known to create situations favouring the development of large populations of reservoir animals such as birds and rodents which support the propagation of zoonotic diseases. Increased industrialization and consequent pollution including disposal of animal waste can create an additional hazard to the human population. A large proportion of zoonotic infections occurs in individuals occupationally engaged in the handling of animals, their carcases or products. These include livestock attendants, farmers, veterinarians and workers employed in factories processing animal products. Infections may also be acquired from the environment, particularly from water contaminated with animal waste. Personnel working with captive wild animals or their tissues are the most likely group to become infected by organisms such as those causing viral haemorrhagic fevers and other exotic infections.

Members of the public may also acquire some infections from pet animals, though these are probably comparatively few in relation to the number of cases arising from the consumption of foods of animal origin. In passing it may be of interest to note that in England and Wales there are no statutory requirements to pasteurize milk from sheep before sale to the general public, which may be a source of chlamydial infection. As a means of reducing the risk of food poisoning two orders were introduced in 1975 in the

UK. Firstly *The Zoonosis Order 1975* (Statutory Instruments 1975), which is designed to facilitate the control of infected animals where *Salmonella* or *Brucella* organisms are a threat to human health, and secondly *The Importation of Processed Animal Protein Order 1981* (Statutory Instruments 1981), which permits the importation of processed animal protein only under the authority of a licence by the Minister of Agriculture.

At the present time *Salmonella* spp. and *Campylobacter* spp. are the most common organisms isolated from contaminated food products, particularly meats and milk, and the number of infections has tended to increase annually. In England and Wales during the 10 years 1975–1984 there were over 100 000 laboratory-reported salmonella infections, 1·5% of which were associated with serious extra-intestinal complications. During the same time there were over 89 000 laboratory reports of campylobacter infections (Galbraith & Barrett 1986). Though campylobacters are usually a common cause of self-limiting acute enteritis in man, they are occasionally associated with miscarriage. In view of the annual increase in the number of cases it seems possible that, since bacteriaemia is a feature of campylobacter infections (Butzler & Skirrow 1979), there will also be an increase in the number of campylobacter-associated miscarriages following localization and proliferation of the organism in placental tissues, which is a feature of campylobacter infections in experimental animals (Coid *et al.* 1987). Other organisms commonly associated with food poisoning are *Clostridium perfringens, Staphylococcus aureus* and *Bacillus* spp. (Hobbs & Roberts 1987). Infection with *Listeria monocytogenes*, which is capable of transmission to the human fetus via the placenta, has also been traced to the consumption of contaminated food. A listeria epidemic, with seven adults and 34 perinatal cases, was shown to result from the ingestion of coleslaw prepared from cabbages previously fertilized with sheep manure (Schlech *et al.* 1983). In addition to these bacterial pathogens, foods of animal origin may also be infected with helminths and protozoal parasites.

Though contaminated foods represent the principal source of zoonotic infections for most members of the public some diseases may be acquired from pet animals. They can arise from bites or close contact with the animals or with their excreta. According to Galbraith & Barrett (1986), ringworm, toxoplasmosis, psittacosis and pasteurellosis are the most common infections acquired from pets in the UK. Toxocariasis and hydatid disease, though less common, were responsible for 42 deaths between 1974 and 1984 compared with 44 as a result of toxoplasmosis and psittacosis during the same period.

The mortality from zoonotic infections is likely to be only a small proportion of approximately 2000 deaths that occur annually in England and Wales from selected infectious and parasitic diseases (Communicable Disease Statistics 1984). Nevertheless the detrimental effects of zoonoses cannot be ignored, even though the levels of morbidity and mortality from such infections appear to be comparatively low.

C. R. Coid
Division of Comparative Medicine
Clinical Research Centre
Harrow HA1 3UJ

References

Butzler, J. P. & Skirrow, M B. (1979) Campylobacter enteritis. *Clin Gastroenterol* **8,** 737-765

Coid, C R., O'Sullivan, A M. & Doré, C J. (1987) Variations in the virulence, for pregnant guinea-pigs, of campylobacters isolated from man *J Med Microbiol* **23,** 187-189.

Communicable Disease Statistics (1984) Statistical Tables series MB2 No 11, Her Majesty's Stationery Office, London.

Galbraith, N. S. & Barrett, N. J (1986) Emerging zoonoses. *J Small Animal Pract* **27,** 621-647

Hobbs, B. C. & Roberts, D (1987) In *Food Poisoning and Food Hygiene,* 5th edn, Edward Arnold, London.

Schlech, W. F , Lavigne, P M., Bortolussi, R. A *et al.* (1983) Epidemic listeriosis—evidence for transmission by food. *N Engl J Med* **308,** 203-206

Statutory Instruments (1975) No. 1030. Animals The Zoonosis Order 1975, Her Majesty's Stationery Office, London.

Statutory Instruments (1981) No. 677 Animals. The Importation of Processed Animal Protein Order 1981 Her Majesty's Stationery Office, London

World Health Organization (1982) Bacterial and viral zoonoses *Technical Report Series 682.* World Health Organization, Geneva.

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Beta-mimetics in preterm labour: an overview of the randomized controlled trials

JAMES F. KING, ADRIAN GRANT, MARC J. N. C. KEIRSE,
IAIN CHALMERS

Summary. Controversy continues about the use of beta-mimetic drugs in preterm labour. One reason for this is that the adequately controlled trials of these drugs have all been small and have thus provided very imprecise estimates of their effects. We have therefore conducted a 'meta-analysis' using data relating to 890 women who participated in the 16 methodologically acceptable controlled trials of these agents in the treatment of preterm labour. This analysis demonstrates an unequivocal effect of beta-mimetic tocolytic administration in delaying delivery, and this is reflected in a reduction in the frequency of preterm birth and low birthweight. However, no beneficial effect of this treatment on perinatal mortality or severe neonatal respiratory disorders could be detected.

Beta-mimetic tocolytic therapy has now become standard practice in the treatment of preterm labour in many centres (Hendricks 1981), and it is often followed by oral beta-mimetic administration for 'maintenance' of tocolysis. However, opinions still vary about the indications for, and the potential benefits of, these drugs (Keirse 1984*a, b*). This difference of opinion reflects, among other things, the quality of the scientific evidence available on which to base a rational clinical decision.

One of the problems with the available evidence on this topic concerns the clinical relevance of the outcomes measured. Outcomes such as small increases in mean birthweight or length of gestation may achieve statistical significance but may not be clinically important. Fundamental outcome measures such as perinatal mortality and morbidity are obviously much more relevant but have not been addressed adequately (Milner *et al.* 1984). Another problem is that much of the data has been derived not from controlled trials, but from observational studies which are notoriously prone to bias and misinterpretation. There is ample evidence that much of the 'success' claimed in observational studies may not be the result of the drug treatment. For instance, in the largest placebo-controlled trial (Larsen *et al.* 1980) 78% of the women in the control group remained undelivered 48 h after entry into the trial. In studies based on observational data an association of this order could easily have been attributed to the drug treatment.

The first placebo-controlled trial of a beta-mimetic drug in the treatment of preterm labour (Adam 1966) failed to detect any effect of the drug (isoxsuprine) on length of gestation or perinatal mortality. This is not surprising considering the number of patients entered into that trial.

National Perinatal Epidemiology Unit, Radcliffe Infirmary, Oxford OX2 6HE, UK
JAMES F. KING*
ADRIAN GRANT
IAIN CHALMERS

Department of Obstetrics and Gynaecology, University of Leiden, Postbus 9600, 2300 RC Leiden, The Netherlands
MARC J N. C. KEIRSE

* Present address: Department of Obstetrics and Gynaecology, Mater Misericordiae Mothers Hospital, South Brisbane, Queensland, 4101 Australia

Correspondence: Dr A. Grant

However, none of the subsequently conducted controlled trials has been sufficiently large to escape the possibility of either overlooking clinically important effects (beneficial or adverse) or exaggerating the significance of apparent differences between treatment groups. In a review of the controlled trials of drugs used in the prevention and treatment of preterm labour, Hemminki & Starfield (1978) concluded that the evidence available at the time was not convincing enough to justify widespread use of these agents (beta-mimetics in particular) in the treatment of preterm labour.

An overall estimate of the true effects of a treatment can be obtained by combining the results of small randomized trials in a formal overview, or meta-analysis, of similar trials (Yusuf *et al.* 1985). In order to clarify some of the confusion which exists about beta-mimetic therapy, we have conducted a formal overview of the controlled trials in which these agents have been compared with either placebo or no active treatment in the management of preterm labour. Trials that simply compared different beta-mimetic agents, without a control group receiving no active treatment, have not been included.

Materials and methods

Controlled trials of beta-mimetic therapy for preterm labour were identified in the following ways: a search was made of the Oxford Database of Perinatal Trials (Chalmers *et al.* 1986); the reference lists in the published papers were reviewed for other possible trials, and finally, colleagues in the USA, Canada and Europe were canvassed to try to detect other completed but unpublished trials. The methodology of these trials was then reviewed, sometimes after further information had been supplied by the principal investigators.

Studies were included in the overview (meta-analysis) if it was judged that random or quasi-random (e.g. using hospital case record numbers) treatment allocation had been used and that withdrawals after treatment allocation, if any, were unlikely to have introduced bias into the comparison Of the 15 published papers identified, four were excluded for the following reasons. Das (1969) gave no reassurance (confirmed by personal communication) that patient allocation had been at random in his study, and there were inconsistencies in the methods by which the treatments had been given. Csapo & Herczeg (1977) included a substantial proportion of patients in the group allocated to beta-mimetic administration whose treatment had been decided by clinical opinion; it was impossible to separate out the remaining cases and their method of treatment allocation was also unclear. Castren *et al.* (1975) reported a study in which there were three cases in the beta-mimetic group for every two in the control group, despite the use of 'alternate allocation'. Merkatz *et al.* (1980) combined a number of trials in a way which made the results impossible to interpret. Subjects entered into trials of *oral* beta-mimetic maintenance therapy, all of whom had previously been 'successfully' treated with intramuscular ritodrine, were included in the drug group. Furthermore, the control group contained some patients treated with ethanol The report did, however, contain data from five centres in which intravenous ritodrine or placebo had been randomly allocated to women who were thought to be in preterm labour. The results from only one of these centres (Spellacy *et al.* 1979) have been published separately. However, the principal investigators in the other four centres (Barden, Hobel, Scommegna & Bieniarz, and Mariona) were contacted and we were subsequently able to gain access to the original data, with the assistance of the company (Duphar) that manufactures the drug.

The meta-analysis, therefore, includes data from 12 published trials and four unpublished trials, the data of which had been included in the analysis conducted by Merkatz *et al.* (1980). These involved a total of 484 beta-mimetic treated women and 406 women treated with placebo and/or 'standard treatment'. The imbalance in the numbers reflects one trial in which placebo was compared with more than one actively treated group. All but one (Cotton *et al.* 1984) of these trials involved the use of oral maintenance therapy after acute tocolysis. Information about the following indices of outcome was sought from the reports of these studies, by letter, by personal contact or by re-examination of the data forms generated for each patient entered into the trials where necessary: (1) Delivery within 24 h of entry to the trial; (2) delivery within 48 h of entry to the trial; (3) delivery before 37 completed weeks gestation; (4) birthweight of less than 2500 g; (5) babies with respiratory distress syndrome or other severe respiratory disorder; (6) perinatal deaths (excluding deaths due to lethal congenital malformations).

The structures of the 16 trials are summarized in Table 1. Twelve studies were of ritodrine therapy and all included oral maintenance if contractions stopped. In 10 of these trials, ritodrine was initially given intravenously, in one, intramuscularly, and in one the allocation was to one of three different ritodrine regimens or to a 'standard' control management. Three trials tested terbutaline, initially given intravenously, and followed by oral maintenance in two. In the remaining trial the beta-mimetic therapy was intramuscular isoxsuprine, followed by oral maintenance.

Methodological quality

In 11 of the 16 trials allocation to treated or control group was stated to have been 'double blind'. In the other five trials the method of random or quasi-random allocation was either not described or was such that selection bias may have operated, thus investigators may have known in advance of entering a participant into the trial to which group she would be allocated.

In 13 of the 16 trials we were able to base our analysis on all cases entered into the trial, and thus control for selection bias after entry, even though this information had often not been published in the original report. In three trials this was not possible, and unfortunately two of these were the two largest trials in the series. Although the cardiovascular effects of beta-mimetic agents make full blinding of treatments difficult, investigators in at least 8 of the 16 trials appeared to have tried hard to achieve blinding. In the other eight trials, assessment (observer) bias is more likely to have operated, although with end-points such as duration of gestation, birthweight and perinatal death this is likely to have been less of a problem than in the assessment of respiratory morbidity.

Statistical methods

Using methods described by Peto *et al* (1976) and Yusuf *et al.* (1985) we analysed information derived from the trials using a procedure which has become known as 'meta-analysis'. This approach is based on expressing as a ratio the odds (chances) of a particular outcome among women allocated to receive the intervention, with the odds (chances) of the same outcome among controls—the odds ratio In each individual trial the odds ratio may be exaggerated or minimized because of the play of chance (especially if the intervention has only a moderate effect, or the sample size is small). But the sum of the differences derived from several independent trials, used in combination with the sum of the variances of the differences, provides a more sensitive test of the effect of the intervention and can be used to calculate a 'typical' odds ratio.

Results

1. Delivery within 24 h of trial entry

Data on delivery within 24 h of trial entry were available for 14 of the 16 studies, and are shown in Table 2. In 13 of the 14 studies there were fewer deliveries in the first 24 h in the group allocated to beta-mimetic therapy than in the control group and in six this was unlikely to reflect chance ($P<0{\cdot}05$). Table 2 and Fig. 1a show the odds ratio and the 95% confidence interval (CI) for each trial The typical odds ratio is 0·29 with 95% CI 0·21 to 0·41. The direction and magnitude of effect is similar in the ritodrine trials (typical odds ratio 0·31; 95% CI 0·21 to 0·45) and the terbutaline trials (typical odds ratio 0·23; 95% CI 0·10 to 0·56).

2. Delivery within 48 h of trial entry

Data on deliveries within 48 h of trial entry (which were available for 12 studies) are shown in Table 3 and summarized in Fig. 1b. There were fewer deliveries within 48 h than expected in nine studies and in three of these the differences were statistically significant ($P<0{\cdot}05$) The typical odds ratio was 0·59 with 95% CI 0·42 to 0·83. The results in the two terbutaline trials were consistent with those in the 10 trials of ritodrine.

3. Delivery before 37 completed weeks

The odds ratio was <1 in 8 of 14 trials for which usable information about preterm delivery was available (Table 4 & Fig. 1c). Overall, however, the typical odds ratio was 0·71 with 95% CI 0·53 to 0·96 and hence is unlikely to reflect chance ($P = 0{\cdot}025$). Again, the results in the terbutaline trials were similar to those in the ritodrine trials.

4. Birthweight below 2500 g

Data from the 13 trials with usable data on low birthweight suggest a beneficial effect of beta-mimetic therapy (Table 5 & Fig. 1d). The typical

Table 1. Description of the 16 trials included in the analysis

Study		Beta-mimetic treatment	Control treatment	Method of allocation	Number of women randomized: number reported on		Outcomes available for analysis
No.	Author				Allocated beta-mimetic	Allocated control	
1	Leveno *et al.* (1986)	Ritodrine (in saline) i.v. + oral maintenance	Saline i.v.	Random by envelopes	54:54	52:52	1, 2, 3, 4, 5, 6
2	Calder & Patel (1985)	Ritodrine (in 5% dextrose) i.v. + oral maintenance	Dextrose i.v.	Hospital casenote number	37:37	39:39	1, 2, 3, 4, 5, 6
3	Larsen *et al.* (1986)	Ritodrine 10 mg i.m. 6 hourly + oral maintenance	Placebo i.m. 6 hourly + oral placebo	Random 'blind' at allocation	63:49	62:50	1, 2, 3, 4, 5, 6
4	Larsen *et al.* (1980)	Ritodrine—i.v. long, —i.v. short, —i.m. + oral maintenance	'Standard' treatment 5% glucose i.v., bedrest, occasional sedatives + placebo maintenance	Random; method unstated	48:41 52:46 50:44 150:131	49:45	1, 2, 3, 4, 5, 6
5	Christensen *et al.* (1980)	Ritodrine i.v. + oral maintenance	Placebo i.v. + placebo maintenance	Random 'blind' at allocation	14:14	16:16	1, 2, 3, 4, 5, 6
		(all ruptured membranes)					
6	Spellacy *et al.* (1979)	Ritodrine i.v. —> i.m.—> oral maintenance	Similar placebo regimen	Random 'blind' at allocation	14:14	15:15	1, 2, 3, 4, 5, 6
7	T. P. Barden (unpublished*)	Ritodrine i.v. —> i.m —> maintenance	Similar placebo oralregimen	Random 'blind' at allocation	12:12	13:13	1, 2, 3, 4, 5, 6
8	C. J. Hobel (unpublished*)	Ritodrine i.v. —> i m. —> maintenance	Similar placebo oralregimen	Random 'blind' at allocation	16:16	15:15	1, 2, 3, 4, 5, 6

*Data previously published in part in Merkatz *et al.* (1980).

Table 1. Continued

Study					Number of women randomized: number reported on		
No	Author	Beta-mimetic treatment	Control treatment	Method of allocation	Allocated beta-mimetic	Allocated control	Outcomes available for analysis
9	A Scommegna (unpublished*)	Ritodrine i.v —> i.m —> oral maintenance	Similar placebo regimen	Random 'blind' at allocation	15:15	17:17	1, 2, 3, 4, 5, 6
10	F G. Mariona (unpublished*)	Ritodrine i.v. —> i m.—> oral maintenance	Similar placebo regimen	Random 'blind' at allocation	5:4 Six other cases unreported—allocation unknown	6·5	1, 2, 3, 4, 5, 6
11	Sivasamboo (1972)	Ritodrine i.v. + oral maintenance	Librium i.m.	Random 'blind selection'	33:33	32:32	3, 4
12	Wesselius de Casparis *et al* (1971)	Ritrodrine i v + oral maintenance	Similar placebo regimen	Random 'blind' at allocation	33:33	30·30	1, 3, 6
Total no of women in ritodrine trials					446:412	346:329	
13	Cotton *et al* (1984)	Terbutaline i.v.	5% dextrose in lactated Ringer's solution i v.	Random; method not stated	19:19	19:19	1, 2, 3, 4, 5, 6
14	Howard *et al* (1982)	Terbutaline i v —> s.c. —> oral maintenance	Similar placebo regimen	Random 'blind' at allocation	16:16	21:21	1, 2, 3, 4, 5, 6
15	Ingemarsson (1976)	Terbutaline i v —> oral maintenance	Similar placebo regimen	Random 'blind' at allocation	15:15	15.15	1, 3, 4, 5, 6
Total no of women in terbutaline trials					50:50	55:55	
16	Adam (1966)	Isoxsuprine i.m. —> oral maintenance	Similar placebo regimen	Random 'blind' at allocation	24:22	24:22	6
Total number of women in all trials					520:484	425:406	

*Data previously published in part in Merkatz *et al* (1980).

Table 2. Delivery within 24 h of trial entry

No.	Trial	Allocated beta-mimetic	Allocated control	Odds ratio	95% CI	*P* (two-tailed)
1	Leveno *et al.* (1986)	15/54 (28%)	25/52 (48%)	0·42	0·19 to 0·92	<0·05
2	Calder & Patel (1985)	4/37 (11%)	9/39 (23%)	0·40	0·11 to 1·42	NS
3	Larsen *et al.* (1986)	5/49 (10%)	16/50 (32%)	0·24	0·08 to 0·69	<0·01
4	Larsen *et al.* (1980)	11/131 (8%)	6/45 (13%)	0·60	0·21 to 1·71	NS
5	Christensen *et al.* (1980)	0/14 (0%)	6/16 (37%)	0·07	0·01 to 0·87	<0·05
6	Spellacy *et al.* (1979)	6/14 (43%)	11/15 (73%)	0·27	0·06 to 1 29	NS
7	Barden	0/12 (0%)	8/13 (62%)	0·03	0·01 to 0·35	0·005
8	Hobel	2/16 (12%)	3/15 (20%)	0·57	0·08 to 4·08	NS
9	Scommegna	1/15 (7%)	5/17 (29%)	0·17	0·02 to 1·45	NS
10	Mariona	0/4 (0%)	0/5 (0%)	—	—	—
12	Wesselius de Casparis *et al.* (1971)	6/33 (18%)	15/30 (50%)	0·22	0·07 to 0·67	0·008
13	Cotton *et al.* (1984)	6/19 (32%)	11/19 (58%)	0·34	0·09 to 1·27	NS
14	Howard *et al.* (1982)	2/15 (13%)	2/18 (11%)	1·23	0·15 to 10·27	NS
15	Ingemarsson (1976)	0/15 (0%)	10/15 (67%)	0·02	<0 01 to 0·19	0·001
	'Typical'			0·29	0·21 to 0·41	<0·00001

CI, Confidence interval.

Table 3. Delivery within 48 h of trial entry

No.	Trial	Allocated beta-mimetic	Allocated control	Odds ratio	95% CI	*P* (two-tailed)
1	Leveno *et al.* (1986)	17/54 (31%)	29/52 (56%)	0·36	0·16 to 0·80	0·012
2	Calder & Patel (1985)	10/37 (27%)	12/39 (31%)	0·83	0·31 to 2·25	NS
3	Larsen *et al.* (1986)	5/49 (10%)	17/50 (34%)	0·22	0 08 to 0·63	0·005
4	Larsen *et al.* (1980)	29/131 (22%)	10/45 (22%)	1·00	0·44 to 2·25	NS
5	Christensen *et al.* (1980)	7/14 (50%)	9/16 (55%)	0·78	0·18 to 3·36	NS
6	Spellacy *et al* (1979)	8/14 (57%)	11/15 (73%)	0·48	0·10 to 2·34	NS
7	Barden	2/12 (17%)	9/13 (69%)	0·09	0·01 to 0·55	0·01
8	Hobel	6/16 (37%)	3/15 (20%)	2·40	0·47 to 12·20	NS
9	Scommegna	6/15 (40%)	7/17 (41%)	0·95	0·23 to 4·01	NS
10	Mariona	2/4 (50%)	1/5 (20%)	4·00	0·19 to 83·44	NS
13	Cotton *et al.* (1984)	9/19 (47%)	12/19 (63%)	0·52	0·40 to 1·94	NS
14	Howard *et al* (1982)	2/15 (13%)	2/18 (11%)	1·23	0·15 to 10·27	NS
	'Typical'			0·59	0·42 to 0·83	0·003

CI, Confidence interval

odds ratio of 0·75 for low birthweight is not quite statistically significant (95% CI 0·55 to 1·02; $P = 0·07$).

5. Respiratory distress syndrome or severe respiratory problems

Usable data related to respiratory problems in the newborn were obtained for 12 trials and these are shown in Table 6 and summarized in Fig. 1e. As can be seen in Table 6 the odds ratios for seven trials are >1, and for five they are <1. The typical odds ratio of 1·07 is a further indication of the lack of any clear direction of effect and the wide 95% CI reflects the relatively small number of infants with neonatal respiratory problems on which these estimates are based. Only 4 of the 12 trial reports used for this analysis indicated whether or not corticosteroids had been given before delivery. The two reports that made it clear that at least some women had received corticosteroids yielded a comparable

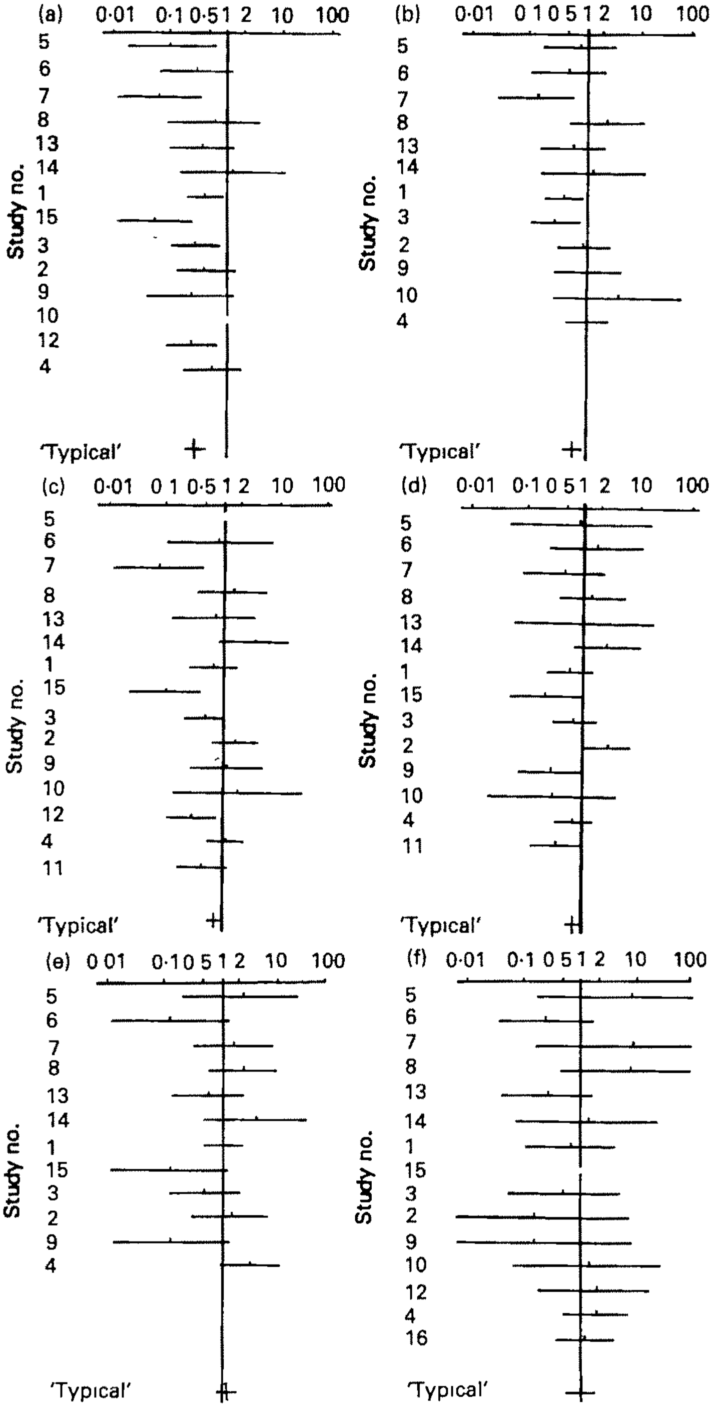

Fig. 1. Effects of beta-mimetic tocolytics in preterm labour. (a) delivery within 24 h (Table 2), (b) delivery within 48 h (Table 3); (c) delivery before 37 completed weeks gestation (Table 4), (d) birthweight less than 2500 g (Table 5); (e) respiratory distress syndrome or severe respiratory problems (Table 6), (f) perinatal death (Table 7) The study numbers are identified on the Tables, the studies are ranked in order of methodological quality ——|—— indicates the odds ratio with the 95% confidence interval

Table 4. Delivery before 37 completed weeks gestation

No.	Trial	Allocated beta-mimetic	Allocated control	Odds ratio	95% CI	*P* (two-tailed)
1	Leveno *et al.* (1986)	40/54 (74%)	42/52 (81%)	0·68	0·27 to 1·70	NS
2	Calder & Patel (1985)	23/37 (62%)	19/39 (49%)	1·73	0·70 to 4·30	NS
3	Larsen *et al.* (1986)	14/49 (29%)	23/50 (46%)	0·47	0·20 to 1·08	NS
4	Larsen *et al.* (1980)	65/131 (50%)	21/45 (47%)	1·13	0·57 to 2·22	NS
5	Christensen *et al.* (1980)	14/14 (100%)	16/16 (100%)	—	—	—
6	Spellacy *et al.* (1979)	12/14 (86%)	13/15 (87%)	0·92	0·11 to 7·91	NS
7	Barden	6/12 (50%)	13/13 (100%)	0·05	0·04 to 0·72	0·015
8	Hobel	10/16 (62%)	8/15 (53%)	1·46	0·34 to 6·24	NS
9	Scommegna	10/15 (67%)	10/16 (62%)	1·20	0·27 to 5·37	NS
10	Mariona	3/4 (75%)	3/5 (60%)	2·00	0·10 to 41·72	NS
11	Sivasamboo (1972)	14/33 (42%)	20/32 (62%)	0·44	0·16 to 1·20	NS
12	Wesselius de Casparis *et al.* (1971)	13/33 (31%) (<38 weeks)	21/30 (70%) (<38 weeks)	0·28	0·10 to 0·78	0·015
13	Cotton *et al.* (1984)	15/19 (79%)	16/19 (84%)	0·70	0·13 to 3·74	NS
14	Howard *et al.* (1982)	9/15 (60%)	5/18 (28%)	3·90	0·91 to 16·67	NS
15	Ingemarsson (1976)	3/15 (20%)	12/15 (80%)	0·06	0·01 to 0·34	0·002
	'Typical'			0·71	0·53 to 0·96	0·025

CI, Confidence interval.

Table 5. Birthweight below 2500 g

No.	Trial	Allocated beta-mimetic	Allocated control	Odds ratio	95% CI	*P* (two-tailed)
1	Leveno *et al.* (1986)	41/56 (73%)	46/55 (84%)	0·53	0·21 to 1·35	NS
2	Calder & Patel (1985)	24/37 (65%)	15/39 (38%)	2·95	1·17 to 7·43	0·02
3	Larsen *et al* (1986)	13/49 (26%)	17/50 (34%)	0·70	0 29 to 1·67	NS
4	Larsen *et al.* (1980)	39/131 (30%)	17/45 (38%)	0·70	0·34 to 1·42	NS
5	Christensen *et al.* (1980)	13/14 (93%)	15/16 (94%)	0·87	0·05 to 16·02	NS
6	Spellacy *et al.* (1979)	13/15 (87%)	12/15 (80%)	1·63	0·23 to 11·72	NS
7	Barden	7/12 (58%)	10/13 (77%)	0·42	0·07 to 2·40	NS
8	Hobel	10/17 (59%)	8/16 (50%)	1·43	0·35 to 5·77	NS
9	Scommegna	5/16 (31%)	11/17 (65%)	0·25	0·06 to 1·05	NS
10	Mariona	2/4 (50%)	4/5 (80%)	0·25	0·01 to 5·22	NS
11	Sivasamboo (1972)	12/32 (37%)	21/32 (66%)	0·31	0·11 to 0·87	0·026
13	Cotton *et al.* (1984)	18/19 (95%)	18/19 (95%)	1·00	0·06 to 16·61	NS
14	Howard *et al.* (1982)	9/16 (56%)	7/21 (33%)	2·57	0·67 to 9·88	NS
15	Ingemarsson (1976)	4/15 (27%)	10/15 (67%)	0·18	0·04 to 0·85	0·03
	'Typical'			0·75	0·55 to 1·02	NS

CI, Confidence interval.

odds ratio for neonatal respiratory morbidity to that derived from all 12 trials, but a with a much wider confidence interval.

6. *Perinatal death*

Information about perinatal deaths (Table 7 & & Fig. 1f) was available for all the trials except one. Of the 14 with usable data, eight had odds ratios >1 and six had odds ratios <1. The typical odds ratio (0·96) was close to unity, but has a wide 95% CI (0·55 to 1·68).

Discussion

This analysis confirms that beta-mimetic drug treatment is more effective than placebo or 'standard treatment' in delaying delivery after preterm labour. The most marked effect is seen in postponement of delivery for 24 h. The treat-

Table 6. Respiratory distress syndrome or severe respiratory problems

No.	Trial	Allocated beta-mimetic	Allocated control	Odds ratio	95% CI	*P* (two-tailed)
1	Leveno *et al.* (1986)	25/56 (45%)	24/55 (44%)	1·04	0·50 to 2·14	NS
2	Calder & Patel (1985)	4/37 (11%)	3/39 (8%)	1·45	0·30 to 6·90	NS
3	Larsen *et al.* (1986)	3/49 (6%)	6/50 (12%)	0·48	0·11 to 2·00	NS
4	Larsen *et al* (1980)	15/131 (11%)	1/45 (2%)	5·69	0·90 to 35·80	NS
5	Christensen *et al.* (1980)	2/14 (14%)	1/16 (6%)	2·50	0·21 to 30·32	NS
6	Spellacy *et al.* (1979)	0/14 (0%)	3/15 (20%)	0·19	0·01 to 3·39	NS
7	Barden	5/12 (42%)	4/13 (31%)	1·61	0·30 to 8·57	NS
8	Hobel	9/17 (53%)	5/16 (31%)	2·47	0·59 to 10·36	NS
9	Scommegna	0/16 (0%)	3/17 (18%)	0·19	0·01 to 3·35	NS
13	Cotton *et al.* (1984)	4/19 (21%)	6/19 (32%)	0·58	0·13 to 2·54	NS
14	Howard *et al.* (1982)	3/16 (19%)	1/21 (5%)	4·62	0·49 to 43·29	NS
15	Ingemarsson (1976)	0/15 (0%)	3/15 (20%)	0·17	0·01 to 3·07	NS
	'Typical'			1·07	0·71 to 1·61	NS

CI, Confidence interval

Table 7. Perinatal death

No.	Trial	Allocated beta-mimetic	Allocated control	Odds ratio	95% CI	*P* (two-tailed)
1	Leveno *et al.* (1986)	2/56 (4%)	3/55 (5%)	0·64	0·10 to 3·95	NS
2	Calder & Patel (1985)	0/37 (0%)	1/39 (3%)	0·11	0·01 to 9·54	NS
3	Larsen *et al.* (1986)	1/49 (2%)	2/50 (4%)	0·50	0·05 to 5·52	NS
4	Larsen *et al* (1980)	11/131 (8%)	2/45 (4%)	1·97	0·43 to 9·05	NS
5	Christensen *et al.* (1980)	1/14 (7%)	0/16 (0%)	8·52	0·17 to 99·99	NS
6	Spellacy *et al.* (1979)	1/15 (7%)	4/15 (27%)	0·21	0·02 to 1.96	NS
7	Barden	1/12 (8%)	0/13 (0%)	1·09	0·02 to 64·44	NS
8	Hobel	2/17 (12%)	0/16 (0%)	3·00	0·12 to 72·80	NS
9	Scommegna	0/16 (0%)	1/17 (6%)	1·06	0·02 to 60·61	NS
10	Mariona	1/4 (25%)	1/5 (20%)	1·33	0·05 to 37·47	NS
12	Wesselius de Casparis *et al.* (1971)	2/33 (6%)	1/30 (3%)	1·87	0·17 to 20·96	NS
13	Cotton *et al* (1984)	1/19 (5%)	4/19 (21%)	0·21	0·02 to 1·81	NS
14	Howard *et al.* (1982)	1/16 (6%)	1/21 (5%)	1·33	0·07 to 23·81	NS
15	Ingemarsson (1976)	0/15 (0%)	0/15 (0%)	—	—	—
16	Adam (1966)	9/28 (32%)	7/24 (29%)	1·15	0·35 to 3·80	NS
	'Typical'			0·96	0·55 to 1·68	NS

CI, Confidence interval.

ment was also shown to be effective in reducing the frequency of preterm birth and (probably) of low birthweight. In all but one of the trials acute tocolysis was followed by oral maintenance treatment. This component of the beta-mimetic drug administration has been shown in other studies to reduce the number of relapses and time to relapse (Creasy *et al* 1980) and to lengthen the duration of gestation (Brown & Tejani 1981).

These effects on gestational duration and birthweight did not, however, result in a detectable decrease in either perinatal mortality or severe respiratory disorders of the newborn. The lack of any suggestion of an effect on these more significant adverse outcomes challenges many of the claims that have been made in favour of tocolytic drug therapy (Decelle & Vokaer 1972; Chez 1981, Merkatz *et al.* 1980). Even more remarkable is the observation that despite a proliferation of beta-mimetic agents, only three have ever been tested against placebo or 'no treatment'. Only one trial has involved isoxsuprine; terbutaline has been studied in three trials; ritodrine has been assessed in 12 separate trials. Other widely used drugs such as fenoterol and salbutamol (Kubli 1977; Keirse 1984*a*) apparently have never been investigated in placebo-controlled trials. This is surprising in view of the important lessons which we have learned from the previous effects of unvalidated drug administration in pregnancy (Grant & Chalmers 1985).

In a formal overview of trials such as that presented here, factors such as duration of treatment, route of administration, dosage used, and so on, introduce a large measure of heterogeneity. It is reasonable to assume that relatively low doses of a weak beta-mimetic drug will show less tocolytic effect and fewer side-effects than a more powerful compound used at the maximum rate which is tolerated by the mother. It should also be considered, however, that the trials reviewed here represent the totality of all attempts at properly controlled assessment that we could uncover.

What is the clinical significance of a treatment which results in a statistically significant decrease in the frequency of preterm birth unaccompanied by any detectable improvement in perinatal mortality and respiratory morbidity? This picture may reflect the inclusion in the trials of too large a proportion of patients in whom postponement of delivery and prolongation of pregnancy were unlikely to confer any further benefit to the baby. It is easy to understand how a treatment which is effective in stopping preterm labour between 36 and 37 weeks will have little potential for reducing perinatal mortality, although it may well reduce the risks of delivery within 48 h of delivery, delivery before 37 weeks and of infants weighing less than 2500 g at birth. These issues could not be explored in our analysis because the data are inadequate for analyses stratified by gestational age at trial entry. But it is not reasonable to assume that the investigators who conducted the various trials reviewed here would have chosen to incorporate women in their trial for whom they considered that treatment would confer no benefit whatsoever. Thus, the lack of any suggestion of an effect on mortality and respiratory morbidity remains noteworthy, particularly given the clear short-term effect of tocolytic treatment on duration of gestation

Claims that the use of beta-mimetic drugs has a large impact on the perinatal mortality associated with preterm birth (Jung & Lamberti 1982) have undoubtedly been exaggerated. In many centres, 12–15% of all preterm births and as high a proportion as 60–65% of the perinatal mortality associated with preterm birth is attributable to antepartum fetal death and lethal malformations (Rush *et al* 1976; Keirse & Kanhai 1981). More than half of the remaining preterm births are the result of obstetric intervention (induction of labour or caesarean section) and/or are associated with maternal or fetal complications that are generally assumed to preclude any attempts at 'therapeutic' prolongation of pregnancy (Keirse & Kanhai 1981). Overall, not more than a third of preterm births occur in pregnancies uncomplicated by conditions which, rightly or wrongly, have been regarded as contraindications to the use of tocolytic drugs for prolongation of pregnancy (Keirse & Kanhai 1981). The available information suggests that less than 20% of the mortality associated with preterm birth occurs in the kinds of pregnancies that have been studied in trials and that most of that mortality is concentrated in the small minority of pregnancies in which preterm delivery occurs before 32 weeks gestation.

Not only are pregnancies that could in theory benefit from tocolysis very rare, but the data presented above show that a trial with a large number of these rare adverse outcomes would be required in order to assess whether or not beta-mimetic tocolysis has a positive or negative effect. It is important to realize that our results are compatible with an impressive reduction (of up to 45%) in perinatal mortality, but that they are equally compatible with an *increase* in perinatal mortality of up to 70%. The mechanisms by which such an increase could be brought about need not imply any direct adverse effects of the beta-mimetic drugs; they might also result from the effectiveness of beta-mimetic treatment in prolonging pregnancy in cases of, for example, clinically unrecognized placental abruption, severe pregnancy-induced hypertension or intrauterine growth retardation. Prolongation of pregnancy in these circumstances may be contrary to the best interests of mother and baby.

Although it has been suggested that the increased cost of maternal intensive care during tocolysis with beta-mimetic drugs is offset by decreased cost of neonatal intensive care (Korenbrot *et al.* 1984), there are currently no data derived from controlled trials to support this view. The multicentre, placebo-controlled randomized trial of ritodrine currently underway in Canada (Milner *et al.* 1984; J.-M. Moutquin, personal communication) offers the best chance of detecting any effects of beta-mimetic administration on the duration and intensity of neonatal care which may exist. The Canadian trial incorporates a cost effectiveness analysis and a long-term follow-up of surviving infants; its results (assuming a satisfactory sample size is achieved) should help to provide a more rational basis for clinical decisions about using beta-mimetic drugs for tocolysis.

Until that information becomes available, the rare but important maternal adverse effects (King *et al.* 1985) of beta-mimetic administration (including death), and the possible adverse effects of these powerful agents on the developing fetus (Keirse 1984*b*) should be borne in mind whenever they are used. The risks of the more serious maternal side-effects will be reduced if the drugs are administered in such a way that the possibility of fluid overload is avoided. It may well be, however, that the main benefit to be derived from tocolytic therapy is to provide sufficient short-term delay of delivery for other effective measures to be implemented. Such options could include buying time for transfer of the mother to a centre with facilities for obstetric and neonatal intensive care, and for the administration of glucocorticoids to reduce perinatal mortality and morbidity (Crowley 1988).

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References

Adam, G S. (1966) Isoxsuprine and premature labour. *Aust NZ J Obstet Gynaecol* **6**, 294-298

Brown, S. M. & Tejani, N. A (1981) Terbutaline sulphate in the prevention of recurrence of premature labour *Obstet Gynecol* **57**, 22-25.

Calder, A A. & Patel, N. (1985) Are betamimetics worthwhile in preterm labour? In *Preterm Labour and its Consequences* (Beard, R. W. & Sharp, F., eds), Proceedings of the 13th Study Group of the RCOG Royal College of Obstetricians and Gynaecologists, London, pp 209-218.

Castren, O., Gummerus, M & Saarikoski, S (1975) Treatment of imminent premature labour *Acta Obstet Gynecol Scand* **54**, 95-100.

Chalmers, I., Hetherington, J , Newdick, M , Mutch, L., Grant, A., Enkin, M., Enkin, E. & Dickersin, K. (1986) The Oxford Database of Perinatal Trials: developing a register of published reports of controlled trials. *Controlled Clin Trials* **7**, 306-324.

Chez, R. A (1981) Preterm labour: the use of β-mimetics. In *Preterm Labour* (Elder, M. G. & Hendricks, C. H., eds), Butterworths, London, pp 124-147.

Christensen, K. K., Ingemarsson, I., Leideman, T., Solum, H & Svenningson, N. (1980) Effect of ritodrine on labor after premature rupture of the membranes *Obstet Gynecol* **55**, 187-190.

Cotton, D. B., Strassner, H. T , Hill, L M., Schifrin, B. S. & Paul, R. H. (1984) Comparison of magnesium sulphate, terbutaline and a placebo for inhibition of preterm labor. *J Reprod Med* **29**, 92-97.

Creasy, R. K., Golbus, M. S., Laros, R. K., Parer, J. T. & Roberts, J. M. (1980) Oral ritodrine maintenance in the treatment of preterm labour. *Am J Obstet Gynecol* **137**, 212-219.

Crowley, P. (1988) Antenatal corticosteroids. In *Effective Care in Pregnancy and Childbirth* (Enkin, M., Keirse, M. J N. C & Chalmers, I., eds), Oxford University Press, Oxford. In press

Csapo, A. I & Herczeg, J. (1977) Arrest of premature labor by isoxsuprine. *Am J Obstet Gynecol* **129**, 482-491.

Das, R (1969) Isoxsuprine in premature labour. *J Obstet Gynaecol India* **19**, 566-570.

Decelle, J & Vokaer, R. (1972) A clinical trial with ritodrine in threatened premature labour In *Proceedings of the International Symposium on the Treatment of Fetal Risks, Baden, Austria* (Baumgarten, K. & Wesselius de Casparis, A., eds), University of Vienna Medical School, Vienna, pp. 36-38

Grant, A. & Chalmers, I. (1985) Epidemiology in obstetrics and gynaecology—some research strategies for investigating aetiology and assessing the effects of clinical practice. In *Scientific Basis of Obstetrics and Gynaecology* (Macdonald, R. R., ed.), Churchill Livingstone, London, pp. 49-84

Hemminki, E. & Starfield, B (1978) Prevention and treatment of premature labour by drugs: a review of controlled clinical trials *Br J Obstet Gynaecol* **85**, 411-417.

Hendricks, C. H. (1981) The case for nonintervention in preterm labour. In *Preterm Labour* (Elder, M. G & Hendricks, C H., eds), Butterworths, London, pp. 93-123.

Howard, T. E , Killam, A. P., Penny, L. L. & Daniell,

W. C. (1982) A double blind random study of terbutaline in premature labor *Milit Med* **147**, 305-307

Ingemarsson, I. (1976) Effect of terbutaline on premature labor A double-blind placebo-controlled study. *Am J Obstet Gynecol* **125**, 520-524.

Jung, J & Lamberti, G. (eds) (1982) *Betamimetic Drugs in Obstetrics and Perinatology.* Georg Thieme, Stuttgart.

Keirse, M. J. N. C (1984*a*) A survey of tocolytic drug treatment in preterm labour. *Br J Obstet Gynaecol* **91**, 424-430.

Keirse, M J N. C. (1984*b*) Betamimetic drugs in the prophylaxis of preterm labour extent and rationale of their use *Br J Obstet Gynaecol* **91**, 431-437

Keirse, M. J N C. & Kanhai, H. H. H. (1981) An obstetrical viewpoint on preterm birth with particular reference to perinatal morbidity and mortality. In *Aspects of Perinatal Morbidity* (Huisjes, H J , ed), Universitaire Boekhandel Nederland, Groningen, pp 1-35.

Korenbrot, C. C., Aalto, L. H & Laros, R K. (1984) The cost-effectiveness of stopping pre-term labour with beta-adrenergic treatment. *N Engl J Med* **310**, 691-696.

King, J. F., Keirse, M. J N C , Grant, A & Chalmers, I (1985) Tocolysis—the case for and against. In *Preterm Labour and its Consequences* (Beard, R. W & Sharp, F , eds) Proceedings of the 13th Study Group of the RCOG Royal College of Obstetricians and Gynaecologists, London, pp 199-208

Kubli, F (1977) In *Pre-term Labour—Proceedings of the Fifth Study Group of the Royal College of Obstetricians and Gynaecologists* (Anderson, A., Beard, R., Brudenell, M J. & Dunn, F. M., eds), RCOG, London, pp 218-220.

Larsen, J. F , Kern Hansen, M., Hesseldahl, H., Kristoffersen, K., Larsen, P. K , Osler, M., Weber, J., Eldon, K & Lange, A (1980) Ritodrine in the treatment of preterm labour A clinical trial to compare a standard treatment with three regimens involving the use of ritodrine *Br J Obstet Gynaecol* **87**, 949-957

Larsen, J. F., Eldon, K., Lange, A P , Leegaard, M., Osler, M., Olsen, J. S. & Permin, M. (1986) Ritodrine in the treatment of preterm labour—Second Danish Multicenter Study. *Obstet Gynecol* **67**, 607-613

Leveno, K. J., Klein, V. R , Guzick, D. S , Young, D C , Hankins, G. D. V & Williams, M. L (1986) Single-centre randomised trial of ritodrine hydrochloride for preterm labour *Lancet* **i**, 1293-1296.

Merkatz, I. R , Peter, J. B. & Barden, T. P (1980) Ritodrine hydrochloride· a beta-mimetic agent for use in preterm labor. II Evidence of efficacy *Obstet Gynecol* **56**, 7-12.

Milner, R A., Enkin, M. W. & Mohide, P T. (1984) The importance of clinical trials in preterm labour *Clin Obstet Gynecol* **27**, 606-613

Peto, R , Pike, M C., Armitage, P *et al* (1976) Design and analysis of randomised clinical trials requiring prolonged observation for each patient. Introduction and design. *Br J Cancer* **34**, 585-612.

Rush, R. W., Keirse, M. J N C., Howat, P., Baum, J. D., Anderson, A. B. M & Turnbull, A C (1976) Contribution of preterm delivery to perinatal mortality. *Br Med J* **ii**, 965-968

Sivasamboo, R. (1972) Premature labour. In *Proceedings of the International Symposium on the Treatment of Fetal Risks, Baden, Austria* (Baumgarten, K. & Wesselius de Casparis, A , eds), University of Vienna Medical School, Vienna, pp 16-20.

Spellacy, W N., Cruz, A. C , Birk, S A. & Buhi, W C. (1979) Treatment of premature labor with ritodrine: a randomized controlled study *Obstet Gynecol* **54**, 220-223

Wesselius de Casparis, A., Thiery, M., Yo Le Sain, A., Baumgarten, K., Brosens, I., Gamisans, O., Stolk, J. G. & Vivier, W. (1971) Results of double-blind, multicentre study with ritodrine in premature labour. *Br Med J* **iii**, 144-147.

Yusuf, S , Peto, R., Lewis, J., Collins, R & Sleight, P. (1985) Betablockade during and after myocardial infarction: an overview of the randomized trials *Prog Cardiovasc Dis* XXVII, **5**, 335-371

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Insulin sensitivity in third trimester pregnancy. A randomized study of dietary effects

R. B. FRASER, F. A. FORD, G. F. LAWRENCE

Summary. The metabolic effects of three diets were investigated in a randomized study in 15 non-pregnant women and 14 pregnant women in the third trimester; all the women were of normal weight. After 2-week periods of habituation to each diet, metabolic profiles were performed on standardized intakes. Diet 1 contained 40% of energy as carbohydrate and 10 g dietary fibre representing typical Western intakes. Diet 2 contained 40% energy as carbohydrate and 52 g dietary fibre and diet 3 contained 60% of energy as carbohydrate and 84 g dietary fibre, representing typical developing world intakes. No deterioration in glucose homeostasis in pregnancy was seen on any of the three diets in contrast to previous work. On diet 1 there was a loss of insulin sensitivity in pregnancy, but not on diets 2 and 3. The loss of insulin sensitivity which is typical of Western women in the third trimester of pregnancy and is considered to be physiological, may be a diet-induced artefact.

There is considerable adaptation of maternal homeostatic mechanisms in pregnancy. This usually occurs in early pregnancy and is presumed to favour fetal growth and development (Hytten 1983). Glucose appears to be unique amongst water soluble nutrients in that the maternal plasma level is raised in the post-prandial period, but falls below the non-pregnant level in the post-absorptive phase and during overnight fasting (Hytten 1983; Cousins *et al.* 1980). These changes are most obvious in the third trimester, when the pregnant woman is also relatively hyperinsulinaemic in response to glucose loading (Lind *et al.* 1973), mixed meals administered as liquid formula diet (Phelps, Metzger & Freinkel 1981) and normal diets (Cousins *et al.* 1980). The paradox of raised post-prandial insulin levels being accompanied by raised plasma glucose levels has been explained by the development of insulin resistance in late pregnancy—the so-called 'diabetogenic effect' of pregnancy. No satisfactory explanation for the insulin resistance has been found (Kühl 1985) although some consider it to be a post-receptor phenomenon (Ryan *et al.* 1985).

Two hypotheses have been generated to explain the changes in glucose homeostasis (Freinkel *et al.* 1979). The first, 'facilitated anabolism', suggests that the relative hyperglycaemia in the post-prandial phase in the pregnant woman is a device to encourage fetal growth, by allowing an increased transfer of maternal plasma glucose to the fetus. The second, 'accelerated starvation', suggests that the lower maternal plasma glucose levels in the post-absorptive phase, and during overnight or more prolonged fasting, lead to enhanced lipolysis. The maternal organism metabolizes fats, thus sparing glucose for transfer across the placenta for fetal growth and metabolism.

Longitudinal studies have suggested that whilst maternal lipogenesis is a feature of the first 30 weeks of pregnancy, lipolysis is a feature of the last 10 (McDonald-Gibson *et al.* 1975). A

University Department of Obstetrics and Gynaecology, Clinical Sciences Centre, Northern General Hospital, Sheffield S5 7AU
R. B. FRASER *Senior Lecturer*
F. A. FORD *Research Dietician*
G. F. LAWRENCE *Research Fellow*

Correspondence R. B. Fraser

Table 1. Nutritional contents of standardized diets

	Energy (kcal)	Percentage of energy as Protein	Fat	Carbohydrate	Dietary fibre (g)
Diet 1	1830	20	39	41	10
Diet 2	1820	22	38	40	52
Diet 3	1850	17	16	60	84

related phenomenon is the net deposition of maternal fat store during pregnancy which in European women results in an average gain of approximately 3·5 kg (Hytten 1980).

All these observations and hypotheses invoke an alteration in insulin sensitivity in the latter half of pregnancy. Insulin sensitivity may be enhanced by high 'dietary fibre' diets (Mann 1984). A low 'dietary fibre' diet may be presumed to have the opposite effect. We have previously confirmed that a high fibre diet in late pregnancy increases insulin sensitivity and that habituation to such a diet is accompanied by improved glucose homeostasis in the third trimester (Fraser 1983; Fraser *et al.* 1983). In a study of well-nourished African women, presumed to be habituated to high fibre intakes, we demonstrated improved glucose homeostasis in response to glucose loading in pregnancy, with no 'diabetogenic effect' demonstrated in the third trimester (Fraser 1981).

Our hypothesis was that if we compared the effects on diurnal plasma glucose and insulin levels in women in the third trimester with those in non-pregnant women, we might see the expected deterioration in post-prandial glucose homeostasis when the women were habituated to a low fibre diet. Habituation to a high dietary fibre diet might lead to enhanced insulin sensitivity, and reduce or abolish this deterioration. We studied intermediary metabolites for two reasons. Levels of blood glycerol and β-hydroxybutyrate would reflect lipolysis rates and be an indirect measure of insulin activity within the adipocyte. Raised levels of both might suggest a reduction in insulin sensitivity. Secondly if any effects on plasma glucose and insulin levels seen on high dietary fibre diets were associated with malabsorption, again lipolysis would be encouraged and the levels of glycerol and β-hydroxybutyrate should rise.

The present randomized crossover study was designed to compare the effects of three diets on insulin sensitivity within and between groups of normal weight non-diabetic, non-pregnant women and pregnant women in the third trimester.

Subjects and methods

A group of 15 non-diabetic, non-smoking, non-pregnant women were recruited mainly from the staff of the Jessop Hospital for Women, Sheffield They were between 18 and 40 years of age and weighed between 90 and 110% of ideal body weight (Metropolitan Life Assurance Co. 1959). Fourteen pregnant women with similar selection criteria, applying a weight correction for the stage of gestation, were recruited from the antenatal clinics of the same hospital. They followed the protocol from 30 weeks gestation.

Each subject was randomized by a sealed envelope system to one of three dietary patterns: diet 1 constituted a 'normal European' intake; diet 2 comprised a normal European intake, but with high fibre carbohydrate sources replacing processed foods and simple sugars, and diet 3 represented a 'normal African' intake with the bulk of energy available from complex carbohydrates. The women were asked to follow the dietary pattern for 2 weeks. Explanatory booklets and recipe suggestions accompanied the advice. At the end of the 2-week period they were admitted fasting at 08·30 hours and spent a day in the research unit, where they ate standardized meals to correspond with the dietary pattern of randomization. The nutritional content of these standardized diets is summarized in Table 1. These were taken as breakfast (08·30 hours), mid-morning snack (10·30 hours), mid-day meal (12·30 hours), mid-afternoon snack (15·30 hours) and evening meal (17·30 hours). These meals were as far as possible equicalorific between the three diets, and for diets 1 and 2 an attempt was made to balance the nutrient proportions. The dietary fibre content of diets 2 and 3 included soluble and insoluble fibre at each main meal.

Blood samples were obtained during each admission, from an indwelling 16-gauge cannula, inserted with local anaesthetic into a suitable forearm vein. The first sample was a fasting specimen at 08·30 hours, subsequent specimens were obtained hourly from 09·00 until 19·00 hours.

After a sampling period, the subjects followed a different dietary pattern for the next 2 weeks, which was determined by the initial randomization in the following sequences: (a) diet 1, 2, 3; (b) diet 2, 3, 1; (c) diet 3, 1, 2. Of the 15 non-pregnant women six were randomized to diet sequence (a), four to (b) and five to (c); of the 14 pregnant women five were randomized to sequence (a), four to (b) and five to (c).

Each subject thus produced three diurnal blood profiles. Profiles were obtained from the pregnant subjects at 32, 34 and 36 weeks gestation.

Sample handling and analysis

At each time-point 5 ml of venous blood was obtained avoiding venous stasis and limb movement. Within 60 s of obtaining the sample, a 1 ml portion was rapidly and accurately measured with a micropipettor into an equal volume of chilled 6% w/v perchloric acid, shaken vigorously and centrifuged, then the supernatant was stored at −20°C. The remaining 4 ml of blood was centrifuged, the plasma separated and stored at −20°C.

Lactate, β-hydroxybutyrate and glycerol were measured in 25-μl portions of the deproteinized whole blood by microfluorimetric adaptation of the methods described by Passonneau (1974), Williamson & Mellanby (1974) and Weiland (1974) respectively. Plasma glucose was measured in a fully automated process using a glucose oxidase technique (YSI Model 23 AM). Plasma insulin levels were measured in 25-μl portions of plasma by radioimmunoassay, using a 'double antibody' method (Hales & Randle 1963).

Levels of plasma glucose, insulin, and intermediary metabolites were compared between pregnant and non-pregnant subjects when consuming identical diets. Statistical analyses used the Mann–Whitney two-tail probability test.

Ethical approval was given for this study by the Sheffield Health Authority Southern District Ethics Commitee, and each subject signed an explanatory consent form.

Results

The diurnal profiles of plasma glucose and insulin on the three diets in pregnant and non-pregnant subjects are shown in Fig. 1. On each diet the post-prandial peak levels of glucose were higher in the non-pregnant subjects and except during the second hour after meals, the diurnal glucose levels were also higher. These changes were accompanied by raised plasma insulin levels in the pregnant subjects throughout the profile.

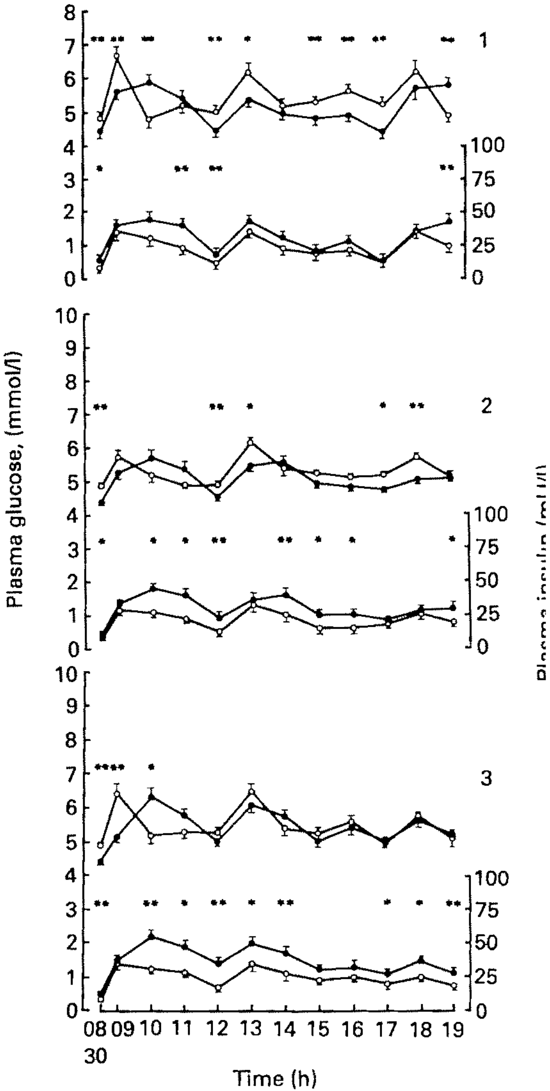

Fig. 1. Diurnal profiles of mean (±SE) plasma glucose levels (mmol/l) (upper lines) and insulin (mUnit/l) (lower lines) on diets 1, 2 and 3 ●—●, Pregnant subjects, ○—○, non-pregnant subjects. Statistical significance of differences *$P<0.05$, **$P<0.01$.

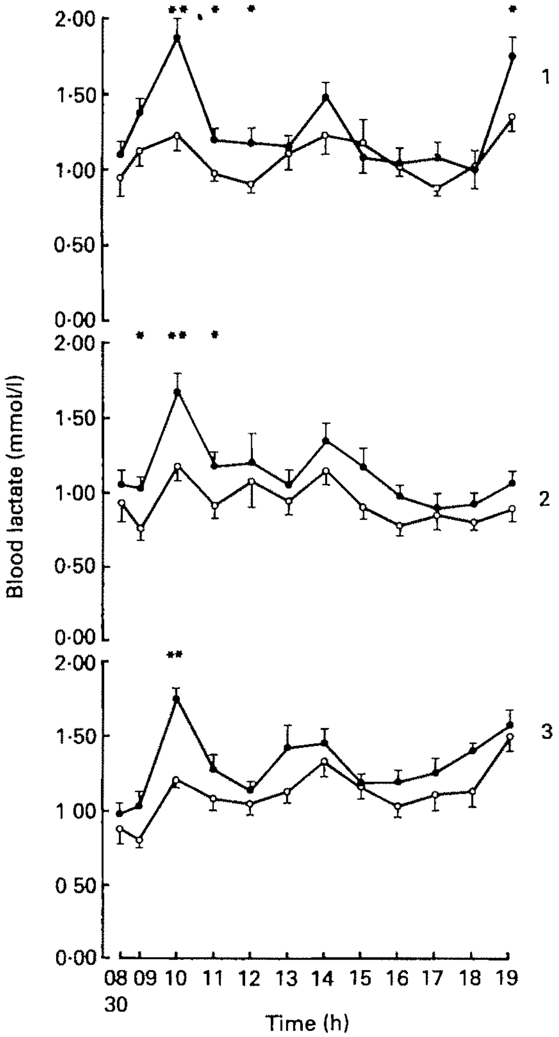

Fig. 2. Diurnal profiles of mean (±SE) blood lactate levels (mmol/l) on three diets 1, 2 and 3 ●—●, Pregnant subjects, ○—○, non-pregnant subjects Statistical significance of differences $^*P<0{\cdot}05$, $^{**}P<0{\cdot}01$.

The diurnal profiles of the intermediary metabolites are shown in Figs 2, 3, 4. Levels of blood lactate were higher in the pregnant subjects, although the absolute levels were higher on the two relatively hyperglycaemic diets, 1 and 2 (Fig. 2). Blood glycerol levels were significantly higher at several time points in the pregnant subjects on diets 1 and 3 but this trend was not significant on diet 2. The absolute levels were lower on both high fibre diets in pregnant and non-pregnant subjects (Fig. 3).

Beta-hydroxybutyrate levels showed a significant relative ketonaemia in pregnancy on diet 1. This was abolished on the two high fibre diets, 2 and 3. Figure 5 shows the within-group comparisons for the non-pregnant and pregnant women. In non-pregnant women on diet 1, β-hydroxybutyrate levels were intermediate between those for diets 2 and 3, whereas in pregnant women on diet 1, β-hydroxybutyrate levels were higher than those for the other two high dietary fibre diets.

Table 2 summarizes the diurnal mean levels of the measured variables

Discussion

On all three diets the paradoxical relation between plasma insulin and glucose levels in pregnancy was abolished It can be seen that the

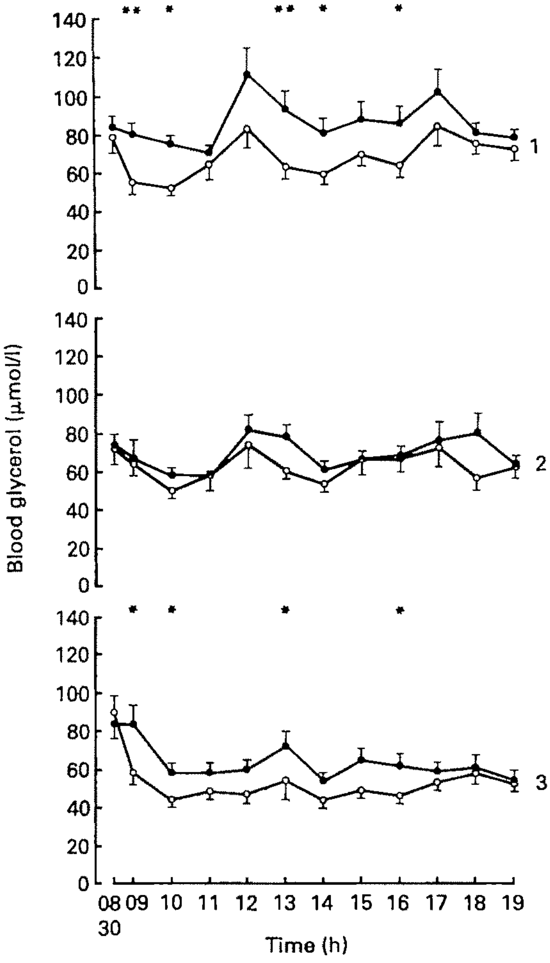

Fig. 3. Diurnal profiles of mean (±SE) blood glycerol levels (μmol/l) on three diets 1, 2 and 3. ●—●, Pregnant subjects, ○—○, non-pregnant subjects. Statistical significance of differences $^*P<0{\cdot}05$, $^{**}P<0{\cdot}01$

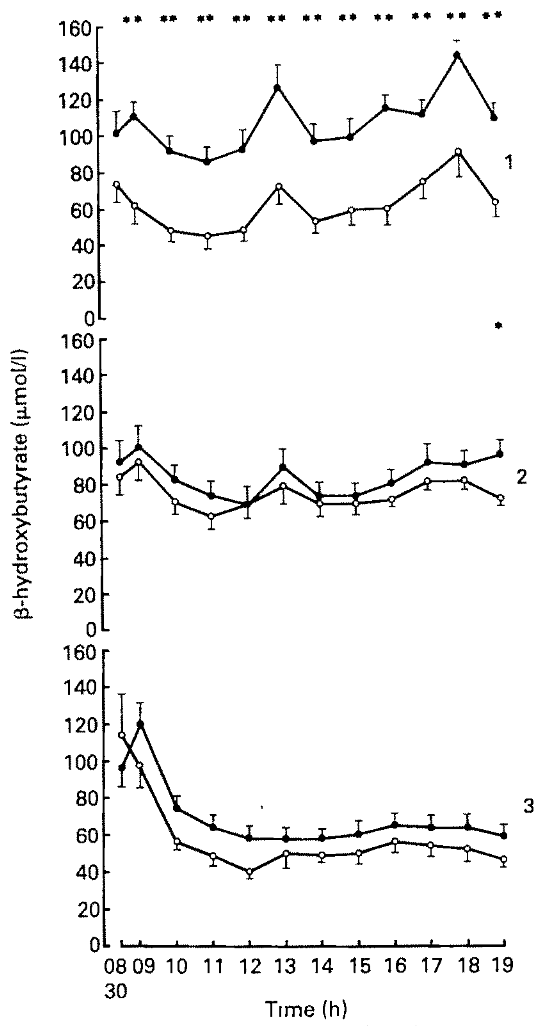

Fig. 4. Diurnal profiles of mean (±SE) blood β-hydroxybutyrate levels (mmol/l) on three diets 1, 2 and 3 ●—●, Pregnant subjects, ○—○, non-pregnant subjects Statistical significance of differences *$P<0{\cdot}05$, **$P<0{\cdot}01$

higher insulin levels are associated with lower glucose levels. The study did not include overnight fasting but in all published studies glucose levels are lower overnight in pregnant than in non-pregnant women (Cousins *et al.* 1980, Phelps *et al.* 1981). This effect would make the difference between the plasma glucose mean values in Table 2 greater. Whilst these results might not represent a significant improvement in glucose homeostasis in the third trimester of pregnancy, they most certainly do not confirm the deterioration which has been accepted as a physiological phenomenon.

Our hypothesis, that the glucose and insulin relations demonstrated in pregnancy by Freinkel's group (Phelps *et al.* 1981) were non-physiological because their subjects were habituated to a low fibre diet, could not be tested. In our study, the low fibre diet (diet 1) produced very different results in pregnant and non-pregnant women, undermining the premise on which the hypothesis was based. There are two explanations of these incompatible results

First, a scrutiny of the paper by Phelps *et al.* (1981) shows that the non-pregnant group failed to demonstrate post-prandial glucose peaks It seemed likely that the liquid formula diet used in their study would lead to rapid absorption of glucose, and it may be that by delaying the first sampling point until 1 h after ingestion, they missed the glucose and insulin peaks in the non-pregnant subjects, but because of slower gastric emptying in pregnancy, the sampling time coincided with the glucose peaks in the pregnant group. To test this possibility we gave a similar liquid formula diet (Fortison–Energy Plus (Cow & Gate); protein 25 g, fat 32·5 g, carbohydrate 90 g in 500 ml) to three non-pregnant volunteers who had fasted overnight. Sampling was per-

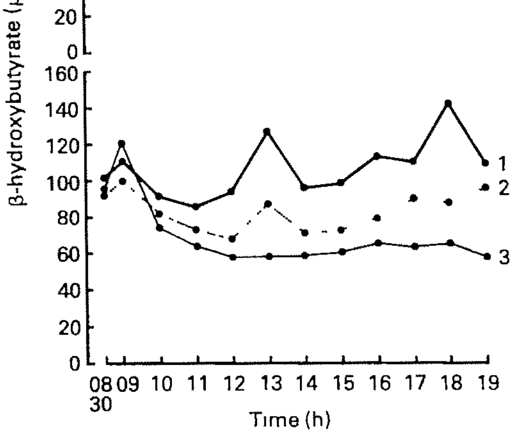

Fig. 5. Within-group studies of mean blood β-hydroxybutyrate levels in non-pregnant (upper figure open circles) and pregnant women (lower figure closed circles) ○—○, Diet 1; ○----○, diet 2, ○—○, diet 3.

Table 2. Diurnal glucose and insulin plasma levels and blood levels of intermediary metabolites in pregnant and non-pregnant women on three different diets

		Mean plasma or blood levels				
Diet	Study group	Glucose (mmol/l)	Insulin (mU/l)	Lactate (mmol/l)	Glycerol (μmol/l)	β-hydroxybutyrate (μmol/l)
1	Pregnant	5·13 (0·85)	30 (16)	1·3 (0·5)	85 (31)	107 (36)
	Non-pregnant	5·42 (0·93)	23 (15)	1·1 (0·4)	67 (28)	62 (37)
2	Pregnant	5·07 (0·68)	29 (16)	1·1 (0·5)	69 (28)	83 (37)
	Non-pregnant	5·28 (0·71)	21 (19)	0·9 (0·4)	63 (29)	74 (31)
3	Pregnant	5·40 (0·85)	36 (18)	1·3 (0·4)	64 (26)	70 (33)
	Non-pregnant	5·50 (0·91)	24 (14)	1·1 (0·4)	54 (25)	60 (41)

Results are mean (SD) values.

formed at 15-min intervals (Fig. 6). As predicted, a curve was described with its peak after 15 min and a relative fall from fasting levels at 60 min; this appears to confirm the possibility of a sampling artefact in the study by Phelps *et al.* (1981).

Second, a fibre-free liquid diet will produce maximal demand for insulin (as does a glucose load) in the first hour after ingestion. If insulin sensitivity is reduced by habituation to a low fibre diet and/or a non-specific post-receptor defect present in late pregnancy (Ryan *et al.* 1985), it may be inadequate to control post-prandial glycaemia. This would lead to an increased area under the curve of glycaemic excursion. A more slowly ingested mixed meal, of normal food sources, may be absorbed at a rate within the secretory capacity of the beta cell mass, leading to a lower peak level of glycaemic excursion, an effect enhanced by the physiological delay in gastric emptying which accompanies pregnancy.

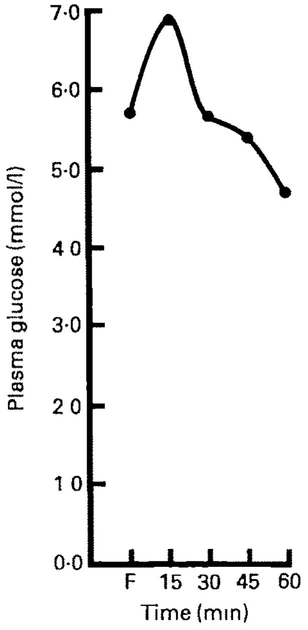

Fig. 6. Mean plasma glucose (mmol/l) response of three non-pregnant subjects to liquid formula diet after overnight fast F, Fasting plasma glucose

Animal models exist which demonstrate alterations in post-receptor insulin sensitivity by dietary manipulation (Tepperman & Tepperman 1985). Habituation to a high fibre diet appears to induce similar enhancement of insulin sensitivity in the human, and this effect may be demonstrated by lipolytic activity, independent of absolute levels of plasma glucose and insulin at the sampling times. This would explain the reduced lipolysis seen on diet 2 as well as the relatively hyperglycaemic/hyperinsulinaemic diet 3. The corollary of this observation is that a low dietary fibre diet may reduce post-receptor insulin sensitivity, as a diet-induced artefact. This raises the uncomfortable possibility that current physiological norms of carbohydrate metabolism in pregnancy, based on studies of healthy women in developed societies, may be incorrect because of such a widespread diet-induced artefact.

The adaptive benefit of a lower mean plasma glucose in pregnancy is speculative. It would not be compatible with the concept of 'facilitated anabolism' (Freinkel *et al.* 1979) One possibility is that it protects the fetus from the unwanted effects of excessive glucose transfer across the placenta. The model of diabetic pregnancy suggests that no other mechanism than maternal glycaemia control exists for this.

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References

Cousins, L , Rigg, L., Hollingsworth, D , Brink, G., Aurand, J. & Yenn, S C. C. (1980) The 24-hour excursion and diurnal rhythm of glucose, insulin and C-peptide in normal pregnancy. *Am J Obstet Gynecol* **136,** 483-487.

Fraser, R. B. (1981) The normal range of the OGTT in the African female: pregnant and non-pregnant. *E Afr Med J* **58,** 90-94.

Fraser, R. B , Ford, F A. & Milner, R.D G. (1983) A controlled trial of a high dietary fibre intake in pregnancy—effects on plasma glucose and insulin levels. *Diabetologia* **25,** 238-241

Fraser, R B. (1983) High fibre diets in pregnancy In *Nutrition in Pregnancy* (Campbell, D. M. & Gillmer, M. D G., eds), RCOG, London, pp 269-277

Freinkel, N , Phelps, R. L & Metzger, B. E (1979) Intermediary metabolism during normal pregnancy. In *Carbohydrate Metabolism in Pregnancy and the Newborn* (Sutherland, H. W. & Stowers, J. M., eds), Springer-Verlag, Berlin, pp 1-31

Hales, C N & Randle, P. J (1963) Immunoassay of insulin with insulin antibody precipitate. *Biochem J* **88,** 137-146

Hytten, F E. (1980) Weight gain in pregnancy In *Clinical Physiology in Obstetrics* (Hytten, F E. & Chamberlain, F., eds), Blackwell Scientific Publications, Oxford, pp. 193-233.

Hytten, F. E (1983) Nutritional physiology during pregnancy In *Nutrition in Pregnancy* (Campbell, D. M. & Gillmer, M. D.G., eds), RCOG, London, pp. 1-8.

Kuhl, C., Hornnes, P. J. & Andersen, O. (1985) Etiology and pathology of gestational diabetes mellitus *Diabetes* **34 (Suppl. 2),** 66-70.

Lind, T., Billewicz, W. Z. & Brown, G. (1973) A serial study of changes occurring in the oral glucose tolerance test during pregnancy. *J Obstet Gynaecol Br Commonw* **80,** 1033-1039.

Mann, J. I. (1984) Lines to legumes. Changing concepts of diabetic diets. *Diabetic Medicine* **I,** 191-198.

McDonald-Gibson, R. G., Young, M. & Hytten, F. E. (1975) Changes in plasma nonesterified fatty acids and serum glycerol in pregnancy. *Br J Obstet Gynaecol* **82,** 460-466.

Metropolitan Life Assurance Company (1959) New weight standards for men and women. *Stat Bull Metropolitan Life Assurance Co.* **40,** 1-4.

Passonneau, J. V. (1974) Lactate: Fluorimetric method. In *Methods of Enzymatic Analysis* (Bergmeyer, H. U., ed), Academic Press, New York, pp. 1468-1472.

Phelps, R. L., Metzger, B. E. & Freinkel, N (1981) Carbohydrate metabolism in pregnancy. XVII· Diurnal profiles of plasma glucose, insulin, free fatty acids, triglycerides, cholesterol and individual aminoacids in late normal pregnancy. *Am J Obstet Gynecol* **140,** 730-736.

Ryan, E. A., O'Sullivan, M. J. & Skyler, J S. (1985) Insulin action during pregnancy. Studies with the euglycaemic clamp technique. *Diabetes* **34,** 380-389.

Tepperman, H M. & Tepperman, J. (1985) Membranes and the response to insulin. *Proc Nutr Soc* **40,** 211-220.

Weiland, O. (1974) Glycerol: UV method. In *Methods of Enzymatic Analysis* (Bergmeyer, H. U., ed.), Academic Press, New York, pp. 1404-1409.

Williamson, D. H & Mellanby, J. (1974) D-(-)-3-hydroxybutyrate. In *Methods of Enzymatic Analysis* (Bergmeyer, H. U., ed.), Academic Press, New York, pp. 1836-1839.

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Pregnancy outcome in elderly primigravidae with and without a history of infertility

SUSAN M. TUCK, P. L. YUDKIN, A. C. TURNBULL

Summary. The pregnancy outcome of 196 primigravidae aged 35 years or over, with no history of involuntary infertility, was compared with that of 196 matched primigravidae aged 20–25 years, and also with 72 'elderly' primigravidae ($\geqslant$35 years) whose pregnancies had followed a period of involuntary infertility of at least 1 year. The older primigravidae with no history of infertility had a four-fold risk of preterm ($<$37 weeks) delivery, a five-fold risk of caesarean section and significantly increased rates of vaginal operative delivery, chronic hypertension and fibroids, when compared with the primigravidae between 20 and 25 years of age. They also showed a greater tendency to severe pre-eclampsia and perinatal death, but these differences were not statistically significant. Elective caesarean section was twice as common in the older women with a history of infertility than in those without such a history (20·8% compared with 10·7%) although this difference was not statistically significant. No other differences in pregnancy outcome were found between the two 'elderly' groups.

The term 'elderly primigravida' is often used loosely in clinical practice, but in 1958 the Council of the International Federation of Obstetricians and Gynaecologists adopted a definition specifying the aee of 35 yeaps or more. Studies dating from several decades ago (Nixon 1931; Miller 1932; Baird & Thomson 1954; MacDonald & MacLennan 1960, Booth & Williams 1964) showed this group of women to be at high risk of complications, including hypertension, fibroids, malpresentations, malpositions, prolonged labour, instrumental deliveries, premature labour, perinatal mortality, light-for-gestational-age babies and impaired lactation. This assessment tends to continue (Donald 1979) although nowadays women of this age are usually in good health.

The recent trend in industrialized countries towards delayed childbearing is thought to reflect the increasing commitment of women to prolonged training and professional employment (Forman *et al.* 1984; Buehler *et al.* 1986). However, among primigravidae aged $\geqslant$35 years there are some in whom pregnancy has followed a period of involuntary infertility. Most reports of pregnancy outcome in 'elderly' primigravidae do not distinguish between these two groups, and thus any characteristics associated with subfertility or its treatment have been combined with those which can be ascribed to advanced maternal age alone. To clarify this point, we have separated 'elderly' primigravidae into two groups: those with and those without a history of infertility.

The purpose of our study was to examine the obstetric outcomes in elderly primigravidae in one maternity hospital over a recent period. We anticipated finding no difference between the babies of 'elderly' and much younger primi-

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Nuffield Department of Obstetrics and Gynaecology, John Radcliffe Hospital, Oxford OX3 9DU
SUSAN M TUCK *Senior Registrar*
P L YUDKIN *Statistician*
A C TURNBULL *Professor*

Correspondence: Susan M Tuck, Department of Obstetrics and Gynaecology, The Royal Free Hospital, London NW3

gravidae, but expected to find that obstetric interventions (especially caesarean section) would be two or three times as common among the older women, particularly those with a history of infertility.

Patients and methods

The Oxford Obstetric Data System has recorded detailed information about all deliveries at the John Radcliffe Hospital since 1978. Miscarriage in women admitted to the hospital's delivery suite (because the gestational age had been judged to be sufficiently advanced to give some hope of fetal survival) are also covered. The System was used to identify all primigravidae delivered at the hospital between 1978 and 1983 who were aged ≥35 years at the time of their booking for antenatal care. A history of miscarriage or induced abortion precluded women from this series. Of the 277 women identified, six had been transferred to the John Radcliffe because of obstetric problems which developed during pregnancy, and they were excluded from the study. Also excluded were three women with multiple pregnancies. Of the remaining 268 women, 72 had a history of involuntary infertility, defined as having taken more than a year to conceive.

The 196 'elderly' primigravidae without a history of infertility were matched for social class (based on the occupation of the woman's partner), smoking habit and year of delivery with a primigravida aged between 20 and 25 years with no history of involuntary infertility. All the elderly primigravidae happened to be of 'Caucasian' ethnic group (as were 95% of the mstetpic patients at the John Radcliffe) and either married or in a stable relationship (as were 94% of the hospital population). The controls were therefore also confined to this ethnic group and marital status. The matched controls were chosen randomly, without knowledge of their pregnancy outcome. All had originally booked for care at the John Radcliffe, or had transferred for non-obstetric reasons.

The three groups in the study were therefore the 196 elderly primigravidae (study group), the 196 matched young primigravidae (control group) and the 72 elderly primigravidae with a history of infertility (subfertile group).

Details of the antenatal, intrapartum and postpartum course of the pregnancies, as well as the neonatal outcome, were obtained from the case notes.

Statistical methods

Comparisons were made between the matched study and control groups and between the unmatched study and subfertile groups.

In the analysis of matched pairs, comparisons between proportions were made using McNemar's test, or for small numbers the binomial test (Siegel 1956). The calculations were thus based on the numbers of discordant pairs. However, for ease of interpretation, the proportions observed, rather than the numbers of discordant pairs, are shown in the tables. To compare proportions in the unmatched groups, the χ^2 test was used, or for small numbers, Fisher's exact test. In each case, relative risk was estimated by the appropriate odds ratio and approximate confidence intervals calculated as described by Fleiss (1981). Comparisons between means were made using the *t*-test, paired or unpaired as appropriate.

Power calculations showed that the numbers in the study and control groups were large enough to detect an increase in rates of obstetric intervention or adverse outcome from 10% to 25%, with 85% power and at a significance level of 0·01. Differences in intervention and complication rates between the study and subfertile groups were, however, unlikely to reach statistical significance.

Results

Maternal characteristics (Table 1)

Women in the study group were heavier and had a higher body mass index (weight/height^2, kg/m^2) than women in the control group. There was a remarkable similarity, however, in the general characteristics of the two groups of 'elderly' primigravidae with and without previous infertility.

In the subfertile group, the average duration of infertility before pregnancy was 5·9 years, 17 (24%) of the group had been infertile for 1–2 years and 10 (14%) had been infertile for more than 10 years. No specific cause had been diagnosed for the infertility in 64% of the group, 18% were anovulatory, 7% had had a fallopian tube problem, in 10% the pathology was in the husband, and one patient had multiple causes

Table 1. Maternal characteristics

	Control group (1) (n = 196)		Study group (2) (n = 196)		Subfertile group (3) (n = 72)	
Variable	n	(%)	n	(%)	n	(%)
Age at booking (years)						
20–25	196	(100·0)	—	(—)	—	(—)
35–36			109	(55·6)	40	(55·6)
37–38			58	(29·6)	19	(26·4)
39–40			19	(9·7)	7	(9·7)
>40			10	(5·1)	6	(8·3)
Social class						
1, 2	123	(62·8)	123	(62·8)	43	(59·7)
3	56	(28·6)	56	(28·6)	22	(30·6)
4, 5	6	(3·1)	6	(3·1)	1	(1·4)
Unclassified	11	(5·6)	11	(5·6)	6	(8·3)
Year of delivery						
1978–80	81	(41·3)	81	(41·3)	28	(38·9)
1981–83	115	(58·7)	115	(58·7)	44	(61·1)
Non-smoker	171	(87·2)	171	(87·2)	58	(80·6)
Height (cm) Mean (SD)	162·7 (5·9)		163·2 (7·1)		162·8 (5·5)	
	(n = 182)		(n = 182)		(n = 69)	
Booking weight (kg) Mean (SD)	61·2 (10·4)**		63·9 (9·4)		62·5 (10·9)	
	(n = 195)		(n = 195)		(n = 65)	
Body mass index (W/H^2, kg/m^2)						
Mean (SD)	23·1 (3·7)**		24·1 (3·2)		23·7 (4·1)	
	(n = 182)		(n = 182)		(n = 62)	

Significance of difference between groups 1 and 2. ** $P < 0·01$

for infertility. Half the group had received no treatment, and 19% had received infertility treatment in the past only, 22% of the group had had ovulatory stimulation before conception and 8% had received various other forms of treatment.

Antenatal factors (Table 2)

Chronic hypertension (defined as blood pressure persistently ≥140/90 mmHg throughout pregnancy) was more common in the study group than in the controls (relative risk 4·0; 95% CI 1·4 to 12·2). However, among chronic hypertensive women, the proportion subsequently developing pre-eclampsia (Chesley 1971) was higher in the control group (75·0% of control group hypertensives compared with 13·0% of study group hypertensives, $P < 0·01$). Among women without chronic hypertension, mild or moderate pre-eclampsia was more common in the control group than in the study group ($P < 0·01$), but the four women with severe pre-eclampsia were all in the study group. There were no differences in the rates of hypertensive disease between the two elderly groups.

Uterine fibroids were much more common in the study group than in the controls, in whom no fibroids were detected, but there was no significant difference in the incidence of fibroids between the study and subfertile groups.

There were no women with endocrine disease in the study group, but there were four in the control group (all with diabetes). In the subfertile group five women had a background of endocrine disease (three with hypothyroidism, one with diabetes and thyrotoxicosis, and one with a pituitary tumour causing hyperprolactinaemia).

Among women undergoing amniocentesis, one abnormal karyotype was detected in the study group (47 XXX) and none in the control group. Fewer of the subfertile women underwent amniocentesis than their fertile contemporaries, but of the 18 having this investigation, two had an abnormal result. Turner's syndrome was detected in one fetus and a balanced translocation in the other.

There were no differences between the three groups in the rates of existing medical disease or

Table 2. Antenatal factors

	Control group (1) (n = 196)		Study group (2) (n = 196)		Subfertile group (3) (n = 72)	
Variable	n	(%)	n	(%)	n	(%)
Gestation at booking (weeks)						
<12	45	(23·0)*	27	(13·8)	13	(18·1)
≥20	32	(16·3)	34	(17·3)	9	(12·5)
Amniocentesis	6	(3·1)***	82	(41·8)	18	(25·0)**
Endocrine disease	4	(2·0)	0	(—)	5	(6·9)**
Fibroids	0	(—)**	8	(4·1)	7	(9·7)
Antepartum haemorrhage	5	(2·6)	6	(3·1)	1	(1·4)
Chronic hypertension						
Total no.	8	(4·1)**	23	(11·7)	9	(12·5)
With superimposed pre-eclampsia†	6	(3·1)	3	(1·5)	0	(—)
No chronic hypertension						
Total no.	188	(100·0)	173	(100·0)	63	(100·0)
Pre-eclampsia						
Mild/moderate	41	(21·8)**	18	(10·4)	10	(15·9)
Severe	0	(—)	4	(2·3)	0	(—)

† Defined according to Chesley (1971)

Significance of difference between groups 1 and 2. *$P < 0{\cdot}05$, **$P < 0{\cdot}01$, ***$P < 0{\cdot}001$.

Significance of difference between groups 2 and 3· **$P < 0{\cdot}01$.

of other antenatal complications not shown in Table 2.

Labour, delivery and postpartum factors (Table 3)

The most striking difference between the study and control groups was in the caesarean section rate: 27·0% in the study group compared with 6·6% in the control group (relative risk 5·4, 95% CI 2·6 to 11·8). There was an increased risk of both elective section (i.e. section planned for a prediagnosed condition) and emergency section.

The two most common indications for the 21 elective sections in the study group were breech

Table 3. Labour, delivery and postpartum factors

	Control group (1) (n = 196)		Study group (2) (n = 196)		Subfertile group (3) (n = 72)	
	n	(%)	n	(%)	n	(%)
Breech/transverse lie	10	(5·1)	17	(8·7)	3	(4·2)
Elective CS	5	(2·6)**	21	10·7	15	(20·8)
Excluding elective CS	191	(100·0)	175	(100·0)	57	(100·0)
Labour induced	69	(36·1)	76	(43·4)	23	(40·4)
CTG monitoring	120	(62·8)*	132	(75·4)	46	(80·7)
Fetal distress diagnosed	22	(11·5)***	49	(28·0)	17	(29·8)
Emergency CS	8	(4·2)***	32	(18·3)	13	(22·8)
Forceps or ventouse	64	(33·5)*	78	(44·6)	30	(52·6)
Vaginal delivery	183	(100·0)	143	(100·0)	44	(100·0)
No analgesia or Entonox only	45	(24·6)	24	(16·8)	9	(20·5)
Episiotomy	133	(72·7)	113	(79·0)	36	(81·8)
Primary PPH	12	(6·6)	14	(9·8)	6	(13·6)

CS, Caesarean section; CTG, cardiotography using ultrasound or fetal scalp electrode; PPH, postpartum haemorrhage.

Significance of differences between groups 1 and 2: *$P < 0{\cdot}05$, **$P < 0{\cdot}01$, ***$P < 0{\cdot}001$.

presentation in 12 and maternal age in four. Four of the five elective sections in the control group were due to breech presentation.

The two most common indications for the 32 emergency sections in the study group were failure to progress in 14 and fetal distress in 13. Of the eight emergency sections in the control group, six were for failure to progress and two were for fetal distress.

The rate of elective caesarean section in the subfertile group was double that in the elderly group without a history of infertility (20·8% compared with 10·7%), but this difference was not statistically significant. The two most common indications for the 15 elective sections in the subfertile group were maternal age in seven and breech presentation in two. There was no difference in the rates of emergency section in the two elderly groups. Of the 13 emergency sections in the subfertile group, six were performed for failure to progress, six for fetal distress and one for brow presentation.

As suggested by the differences in caesarean section rates, fetal distress was more often diagnosed in the study group than in the control group (relative risk 3·0, 95% CI 1·7 to 5·2). The basis for the diagnosis was similar in the two groups, about half being associated with 'late' decelerations in fetal heart rate recordings. There was no difference in the rate of diagnosis of fetal distress between the two elderly groups Continuous electronic fetal heart monitoring during labour was used significantly more often in the two elderly groups than in the younger primigravidae. (The policy in the John Radcliffe is to use continuous fetal heart monitoring with the patient's consent in labours judged to be at high risk of complications, and in other labours at the patient's request.)

The mean length of the first stage of labour was similar in the study group, 8·3 h (SD 4·5), and in the control group, 8·0 h (SD 4·0). However, women in the study group experienced a longer second stage of labour, with a mean of 69·0 min (SD 47·4), compared with a mean of 57·0 min (SD 32·9) in the control group ($P <$ 0·01). There was no difference in the length of the first and second stages of labour between the two elderly groups. The mean length of the first stage of labour in the subfertile group was 7·8 h (SD 4·2), and the mean length of the second stage of labour was 64·8 min (SD 40·9).

For women with vaginal deliveries the episiotomy rates showed no differences between the groups, nor were there any significant differences in the numbers with intact perineums (none in the study group, five in the control group and none in the subfertile group). There was one woman in each of the elderly groups who had a third degree perineal tear, and none in the control group. There were no differences between the groups in the rates of postpartum complications not shown in Table 3, such as manual removal of the placenta, pyrexia and secondary postpartum haemorrhage.

Neonatal outcome (Table 4)

The rate of preterm (<37 weeks) delivery was higher in the study group than in the control group: 6·1% compared with 1·5% (relative risk 4·0; 95% CI 1·1 to 17·9). Low birthweight (<2500 g) was also more common in the study group (8·2% compared with 3·6%) and the mean birthweight was lower, 3225·6 g (SD 626) compared with 3323·6 g (SD 450) in the control group, but the difference in birthweight was not statistically significant. There was no difference between the study and control groups in the number of infants who were light-for-gestational-age. There were also no differences between the two elderly groups in their rates of preterm or low birthweight babies. The mean birthweight in the subfertile elderly group was 3239·8 g (SD 532).

There were two fresh stillbirths and one missed miscarriage in the study group, but none among the controls. One stillbirth (at 40 weeks gestation) resulted from cord prolapse and the other (diagnosed on admission of the patient in labour at 40 weeks gestation) was of unknown cause. The missed miscarriage occurred at 21 weeks' gestation in a woman with multiple large fibroids There were no neonatal deaths in the control group, but one in the study group. The death occurred at 6 h from hyaline membrane disease, in a baby born at 26 weeks gestation with a birthweight of 1080 g. The baby was born 3 weeks after spontaneous rupture of membranes, following amniocentesis. The single perinatal death in the subfertile group was a neonatal death at 3 days of a baby born at 40 weeks gestation with a birthweight of 2900 g. The baby suffered tentorial tears and intra-cranial haemorrhages after birth by Kiellands forceps for fetal distress.

The four congenital malformations in the study group were: ventricular septal defect,

Table 4. Neonatal factors

	Control group (1) (*n* = 196)		Study group (2) (*n* = 196)		Subfertile group (3) (*n* = 72)	
Variable	*n*	(%)	*n*	(%)	*n*	(%)
Gestation at delivery (weeks)*						
≤30	0		2	(1·0)	0	
31–32	0		2	(1·0)	1	(1·4)
33–34	1	(0·5)	5	(2·6)	0	
35–36	2	(1·0)	3	(1·5)	3	(4·2)
37–40	138	(70·4)	156	(79·6)	62	(86·1)
>40	55	(28·1)	28	(14·3)	6	(8·3)
Birthweight (g)						
<500	0		2	(1·0)	0	
500–999	0		0		0	
1000–1499	0		1	(0·5)	0	
1500–1999	0		4	(2·0)	2	(2·8)
2000–2499	7	(3·6)	9	(4·6)	6	(8·3)
2500–2999	42	(21·4)	39	(19·9)	12	(16·7)
3000–3499	70	(35·7)	78	(39·8)	27	(37·5)
≥3500	77	(39·3)	63	(32·1)	25	(34·7)
Small-for-dates (<10th centile)	16	(8·2)	15	(7·7)	7	(9·7)
Stillbirth or late miscarriage	0		3	(1·5)	0	
Early neonatal death	0		1	(0·5)	1	(1·4)
Low Apgar scores						
<4 at 1 min	2	(1·0)	7	(3·6)	3	(4·8)
<7 at 5 min	0		3	(1·5)	1	(1·4)
Intubation for resuscitation for >5 min	2	(1·0)	9	(4·6)	3	(4·2)
Intubation for meconium aspiration	12	(6·1)	14	(7·1)	4	(5·6)
Referral to special care	9	(4·6)	13	(6·6)	7	(9·7)
Congenital malformation	1	(0·5)	4	(2·0)	3	(4·2)
Breast-feeding at discharge	169	(86·2)	162	(82·7)	58	(80·6)

* The rate of preterm delivery was significantly different between groups 1 and 2 ($P < 0{\cdot}05$)

pyloric stenosis with patent ductus arteriosus, talipes calcaneovalgus, and an accessory finger. In the control group one baby was born with Down's syndrome. The three congenital malformations occurring in the subfertile group were: Turner's syndrome (already diagnosed at amniocentesis), transposition of the great vessels, and dislocation of the hip.

Rates of referral to the special care baby unit showed no significant differences between the three groups.

Discussion

During the 6-year period 1978 to 1983, 34·3% of the 33 256 women delivered at the John Radcliffe Hospital were primigravidae and 2·4% of them were ≥35 years of age. This proportion increased steadily from 1·8% in 1978 to 3·0% in 1983.

The impression that the increasing voluntary postponement of first pregnancies is a characteristic of professional and managerial women is reflected in the strong over-representation of women in social classes 1 and 2 in our study group (62·8% of the study group compared with 32·9% of Oxford District residents delivered at the John Radcliffe). There was a corresponding under-representation in our study group of women in social classes 4 and 5 (3·1% compared with 17·4%). The proportion who were non-smokers (87·2%) was also greater than among the Oxford District residents delivered at the John Radcliffe (72·7%). Both these characteristics would be expected to act in favour of the study group and hence were matched for in the controls. However, while the control group exhibited very low rates of all adverse outcomes, the study group did not. The preterm delivery rate in the study group (6·1%) was the same as the rate for all Oxford District residents delivered at the John Radcliffe, while the rate of low birthweight (<2500 g) babies was a little higher (8·2% compared with 6·6%). It was notable that all the fetal losses in the survey occurred in the two elderly groups, although this difference from the control group was not statistically significant.

We found a markedly higher rate of interventions in labour among the elderly groups, which previous studies have also noted (Baird & Thomson 1954; MacDonald & MacLennan 1960; Messinis *et al.* 1982). Although specific obstetric indications were usually involved, the impression was often gained that the woman's age also contributed strongly to the decision to intervene; indeed, maternal age was the primary indication recorded for 11 of the 35 elective caesarean sections in the two elderly groups.

The very high rate of caesarean delivery in the subfertile group is likely also to reflect an understandable feeling on the part of the obstetrician that pregnancies in these circumstances are particularly precious. Similarly, the lesser use of amniocentesis among the subfertile women may indicate their greater readiness to accept the possibility of an abnormal baby. Indeed, the case of Turner's syndrome which was diagnosed at amniocentesis was not aborted, in accord with the parents' wishes.

The umbrella category of 'toxaemia of pregnancy' has been reported in earlier series as being two or three times as common in elderly primigravidae as in younger primigravidae (Miller 1932; MacDonald & MacLennan 1960; Messinis *et al.* 1982), and we have attempted to examine this observation in more detail in our series. The increased rate of chronic hypertension found among the elderly primigravidae may be a result of their heavier build, but is more likely to be due to their age alone. If this is so, then the higher rate of mild or moderate pre-eclampsia found among the younger women may simply be a complementary finding. Many of these women in the younger group may have a baseline blood pressure near to the cut-off point of 140/90 mmHg, and these women will tend to develop chronic hypertension in later years. The higher proportion of chronic hypertensives developing superimposed pre-eclampsia in the 20–25-year-old group suggests that the nature of their hypertensive disease is more serious than that of most of the older women. In contrast, the four women with severe pre-eclampsia who were previously normotensive were all in the older group.

Thus of the pregnancy complications ascribed to elderly primigravidae in earlier studies, our data have confirmed a significantly higher rate of preterm delivery, caesarean section (both elective and emergency), vaginal operative delivery, chronic hypertension and fibroids. We have also observed higher rates of severe pre-eclampsia and perinatal death, but these differences were not statistically significant. Our results do not, however, show any increase in small-for-gestational-age babies or failure to breast-feed.

This study has also illustrated, however, that even for 'elderly' primigravidae a pregnancy following a period of involuntary infertility carries no significant disadvantage in terms of obstetric complications and outcome. Given the important effects of advanced maternal age on the outcome of first pregnancies without a history of infertility, it may be reassuring to subfertile women reaching the age of 35 that their subfertility appears to cause no added risk.

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References

Baird, D & Thomson, A M. (1954) The epidemiological approach in obstetrics *Gynaecologia* **138**, 226-245

Booth, R T. & Williams, G. L (1964) Elderly primigravidae. *J Obstet Gynaecol Br Commonw* **71**, 249-254

Buehler, J. W , Kaunitz, A M., Hogue, C J. R., Hughes, J. M., Smith, J. C. & Rochat, R W. (1986) Maternal mortality in women aged 35 years or older: United States *JAMA* **255**, 53-57.

Chesley, L. C (1971) Hypertensive disorders in pregnancy. In *Williams Obstetrics*, 14th edn (Hellman, L M & Pritchard, J A , eds), Appleton, New York, p. 685.

Donald, I. (ed.) (1979) The elderly primigravida In *Practical Obstetric Problems*, 5th edn, Lloyd-Luke, London, pp. 133-136.

Fleiss, J L. (1981) *Statistical Methods for Rates and Proportions*, 2nd edn, John Wiley & Sons, New York, pp. 71, 115.

Forman, M. R., Meirik, O. & Berendes, H. W. (1984) Delayed childbearing in Sweden. *JAMA* **252**, 3135-3139

MacDonald, I. R. & MacLennan, H. R. (1960) A consideration of the treatment of elderly primigravidae. *J Obstet Gynaecol Br Commonw* **67**, 443-450.

Messinis, I., Malamitsi-Puchner, A., Hadjigeorgiou, E., Lolis, D. & Nicolopoulos, D. (1982) Perinatal complications in elderly primigravidas. *Padiatr Padol* **17**, 597-602.

Miller, D. (1932) The influence of age on process of childbirth; investigation into course of pregnancy and labour in very young and in elderly primipara *Trans Edinburgh Obstet Soc* **52**, 161-172.

Nixon, W. C. W. (1931) The influence of age on labour. *J Obstet Gynaecol Br Emp* **38**, 821-826.

Siegel, S. (1956) *Nonparametric Statistics for the Behavioural Sciences*. McGraw-Hill Kogakusha, Tokyo, p. 63.

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Sex difference in fetal head growth

W. M. O. MOORE, B. S. WARD, V. P. JONES, F. N. BAMFORD

Summary. Growth of the fetal biparietal diameter (BPD) throughout the second and third trimesters was measured in a prospective longitudinal study. Linear-cubic equations were fitted to the data of individual fetuses and from these equations mean growth curves were produced for males and females. The head growth trajectories of males and females were significantly different. The study illustrates why the practice of dating pregnancies by ultrasonic fetal BPD measurement at about 16 weeks gestation can lead to error.

Most descriptions of fetal growth have been obtained from cross-sectional studies and their applicability to individuals is therefore uncertain. Even when growth within a population is relatively consistent, the identification of subgroups with different growth characteristics is possible only by the use of longitudinal data and their analysis by appropriate techniques (Deter *et al.* 1982).

This portion of the Central Manchester Child Growth Project was concerned with fetal head growth in the second and third trimesters. Using longitudinal data derived from measurements spaced at regular intervals the growth of the fetal biparietal diameter (BPD) in each sex and in separate birthweight categories was investigated. The objective was to determine whether or not there are separate subgroups within the population.

Subjects and methods

The study was conducted over 2 years on women who presented for antenatal care before or at the beginning of the second trimester and who were willing to have their entire antenatal care carried out at St Mary's Hospital. Usually three women entered the project each week. When more were available to do so in a particular week, they were not invited to join the project because this would have overloaded facilities for serial ultrasonography. At the end of 2 years, 231 women had entered the project. The booking examination and subsequent examinations were conducted by one person (W.M.O.M.), and detailed records were made of any illnesses, vaginal bleeding episodes, cigarette consumption and medication. Fetal head growth was assessed by serial ultrasound measurements of the BPD of each fetus from the beginning of the second trimester to approximately 38 weeks gestation. From the original 231 subjects, a total of 26 were excluded for the following reasons: miscarriage (6), perinatal death (4), moving from the area (5), and conception occurring before resumption of menstruation following cessation of oral contraception (9), or during an episode of amenorrhoea not associated with oral contraception (2). This left 205 women in the study.

Because precision in gestational age is crucial, the study was restricted to those who were delivered within 7 days of the estimated date of delivery (EDD). An EDD of 280 days from the first day of the last normal menstrual period (LMP) was adjusted to take account of variations in the duration of menstrual cycles. The women were questioned carefully about their menstruation during the year preceding the LMP, the average of the longest and shortest

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St Mary's Hospital, Manchester M13 0JH
W. M. O. MOORE *Reader in Obstetrics and Gynaecology*
B. S. WARD *Experimental Officer*
V. P. JONES *Medical Assistant*
F. N. BAMFORD *Reader in Developmental Paediatrics*

Correspondence: Dr W. M. O Moore

cycles was calculated for each of them and the EDD was adjusted by the number of days the average differed from 28. The analysis of data was restricted to the 109 of 205 women who were delivered within 7 days of the EDD, in 89 of them labour commenced spontaneously.

The method of cephalometry was the combined A and B scan method (Campbell 1968) using a Nuclear Enterprises diasonograph NE 4102 with a probe frequency of 2·5 MHz and a caliper setting of 1600 m/s. All ultrasound measurements were made either by one of the authors (V.P.J.) or her specially trained deputy. Measurements of BPD were planned at 3-week intervals and the average number for each of the 109 fetuses was seven. Any additional measurements made for clinical reasons were not included in the subsequent analysis of data. The one woman who had fewer than the five planned serial measurements was excluded because the number of measurements was inadequate for the fitting of a polynomial of degree 3.

Method of analysis

Polynomial equations for describing head growth permit construction of growth curves for individuals, and may be combined to produce growth curves for different sexes and different birthweight categories within sexes. Fits to the head-growth data of individual fetuses were obtained using linear, linear-quadratic and linear-cubic functions. The linear-cubic model produced the smallest residual sum of squares, and also the smallest coefficients of variation of the polynomial coefficients as noted previously by Deter *et al.* (1982), and was therefore chosen as the optimum model. For each individual fetus this best fit linear-cubic equation was fitted through its serial BPD measurements using non-linear regression analysis (UMRCC 1980) The polynomial used was $y = b_0 + b_1t + b_3t^3$ where y = biparietal diameter, t = gestational age and b_0, b_1, b_3 are coefficients. Using the coefficients b_0, b_1 and b_3 for each fetus, a mean coefficient curve was obtained for each sex. Student's t-tests were used to compare corresponding coefficients from the curves for males and females.

Results

To facilitate comparison with other published data, the absolute mean (SD) values of fetal BPD for males and females at successive gestational ages, using the data as cross-sectional data, are given in Table 1.

From the linear-cubic equation for each fetus, its weekly BPD values were calculated. Mean (SD) values of fetal BPD for males and females at successive gestational ages were then obtained and are given in Table 2.

The mean fetal BPD growth equations for males and females are given in Table 3. The corresponding coefficients b_0, b_1 and b_3 for the fitted equations describing head growth for 54 male and 54 female fetuses were compared separately. Because these coefficients are significantly different, male and female head growth trajectories are significantly different. When the analysis was repeated for 44 male and 45 female fetuses who were born after spontaneous onset of labour, a similar result was obtained.

The mean birthweights for males and females were 3430 (SD 414) g and 3250 (SD 400) g respectively The mean curves from 28 to 38

Table 1. Cross-sectional fetal biparietal diameter mean (SD) values from 13 to 38 weeks gestation

Gestational age (weeks)	Female fetuses		Male fetuses	
	(n=54)	(n)	(n=54)	(n)
13	2·45 (0·35)	11	2·55 (0·38)	15
14	2·78 (0·37)	17	2·77 (0·41)	18
15	3·28 (0·38)	8	3·15 (0·40)	10
16	3·67 (0·27)	18	3·75 (0·29)	15
17	3·97 (0·35)	16	4·09 (0·30)	20
18	4·33 (0·33)	10	4·30 (0·30)	9
19	4·68 (0·24)	20	4·84 (0·32)	21
20	4·97 (0·25)	12	5·14 (0·31)	20
21	5·29 (0·45)	13	5·40 (0·36)	6
22	5·66 (0·29)	24	5·78 (0·36)	18
23	5·95 (0·30)	11	6·11 (0·39)	23
24	6·30 (0·46)	15	6·57 (0·55)	8
25	6·58 (0·30)	23	6·86 (0·23)	14
26	6·80 (0·41)	9	7·05 (0·38)	20
27	7·25 (0·38)	14	7·48 (0·51)	15
28	7·57 (0·26)	19	7·70 (0·35)	15
29	7·70 (0·30)	15	8·01 (0·32)	13
30	7·96 (0·37)	15	8·19 (0·42)	19
31	8·37 (0·14)	10	8·52 (0·35)	17
32	8·64 (0·23)	13	8·75 (0·23)	11
33	8·61 (0·29)	14	8·83 (0·37)	17
34	8·98 (0·25)	15	9·21 (0·28)	18
35	9·25 (0·13)	13	9·31 (0·13)	12
36	9·22 (0·21)	17	9·34 (0·27)	13
37	9·43 (0·21)	11	9·56 (0·34)	16
38	9·53 (0·23)	15	9·62 (0·28)	12

n, Number of fetuses at each age

Table 2. Longitudinal fetal biparietal diameter mean (SD) values from 13 to 38 weeks gestation

Gestational age (weeks)	Female fetuses (*n*=54)	(*n*)	Male fetuses (*n*=54)	(*n*)
13	2·50 (0·30)	11	2·57 (0·35)	15
14	2·83 (0·30)	28	2·87 (0·35)	33
15	3·23 (0·29)	36	3·25 (0·34)	43
16	3·60 (0·26)	45	3·63 (0·31)	50
17	3·96 (0·30)	51	4·02 (0·31)	52
18	4·31 (0·31)	53	4·40 (0·31)	52
19	4·67 (0·30)	53	4·79 (0·33)	53
20	5·01 (0·30)	53	5·15 (0·33)	54
21	5·35 (0·29)	53	5·50 (0·33)	54
22	5·67 (0·30)	54	5·85 (0·34)	54
23	6·00 (0·30)	54	6·18 (0·34)	54
24	6·31 (0·30)	54	6·51 (0·35)	54
25	6·62 (0·30)	54	6·82 (0·35)	54
26	6·92 (0·30)	54	7·13 (0·35)	54
27	7·21 (0·29)	54	7·42 (0·35)	54
28	7·49 (0·29)	54	7·70 (0·35)	54
29	7·75 (0·28)	54	7·96 (0·35)	54
30	8·01 (0·27)	54	8·22 (0·34)	54
31	8·26 (0·26)	54	8·46 (0·34)	54
32	8·49 (0·25)	54	8·68 (0·33)	54
33	8·71 (0·24)	53	8·89 (0·32)	54
34	8·92 (0·23)	53	9·09 (0·31)	52
35	9·11 (0·23)	51	9·25 (0·31)	46
36	9·26 (0·22)	43	9·40 (0·30)	41
37	9·45 (0·23)	26	9·55 (0·30)	28
38	9·57 (0·24)	15	9·64 (0·27)	12

n, Number of fetuses at each age

weeks gestation for each sex in the three birthweight categories 2500–2999 g, 3000–3499 g and 3500–3999 g are illustrated in Fig. 1. Within each birthweight category the BPD values for males were greater than for females (average differences in birthweight categories 2500–2999 g, 3000–3499 g and 3500–3999 g were 1·4 mm, 0·80 mm and 1·5 mm respectively). Using Student's *t*-test to compare corresponding coefficients from the curves for males and females, the difference in head growth trajectories was significant at the 0·05 ($P<0{\cdot}05$) level only in the heaviest birthweight category.

Discussion

The question whether or not male fetuses, as judged from ultrasound crown–rump measurements, are larger than females in the first trimester is not yet resolved (Pedersen 1980; Sebling & McKay 1985; Pedersen & Mantoni 1985). Using cross-sectional data Wald *et al.* (1986) demonstrated a statistically significant sex difference in fetal BPD at weeks 14, 16, 17, 18, 19, 20 and 26 of the second trimester. By the analysis of longitudinal data by appropriate techniques (Deter *et al.* 1982), the present study was able to illustrate that the BPD growth trajectories of the sexes are different throughout the second and third trimesters.

To reduce as far as possible errors in gestational age, the analysis was restricted to the data of those fetuses who were born within 7 days of term (estimated as 280 days from the LMP). The design of the project was such that any operator or machine error is applicable to all readings. The SD values of BPD reported in Table 1 are close to the observations of other authors in early gestation (Flamme 1972; Aantaa & Forss 1974; Sabbagha *et al.* 1976; Wiener *et al.* 1977; Jeanty *et al.* 1984; Wexler *et al.* 1986) and in late gestation (Campbell 1968; Flamme 1972; Aantaa & Forss 1974; Sabbagha *et al.* 1976; Wiener *et al.* 1977; Jeanty *et al.* 1984; Wexler *et al.* 1986). The magnitude of the SD about the mean in the third trimester is due to differences in head size with varying birthweight, as illustrated in Fig. 1. It is of interest to note that in the rhesus monkey the variability in BPD does not change with gestational age (Nyland *et al.* 1984).

The use of longitudinal data and their appropriate analysis has revealed that the variability of fetal BPD measurements about the mean at all

Table 3. Mean (SD) values of the coefficients b_0, b_1 and b_3 for the fitted linear-cubic $y = b_0 + b_1t + b_3t^3$ from 13 to 38 weeks gestation

Population	Number of fetuses	b_0	b_1	b_3
Male	54	−3·2158 (0·8966)	0·4480 (0·0561)	$-7{\cdot}4398\times10^{-5}$ ($2{\cdot}4298\times10^{-5}$)
Female	54	−2·8637 (0·9961)	0·4179 (0·0571)	$-6{\cdot}1594\times10^{-5}$ ($2{\cdot}4678\times15^{-5}$)

Level of significance (*P*) between the sexes for b_0, b_1 and b_3 are 0·056, 0·007 and 0·008 respectively

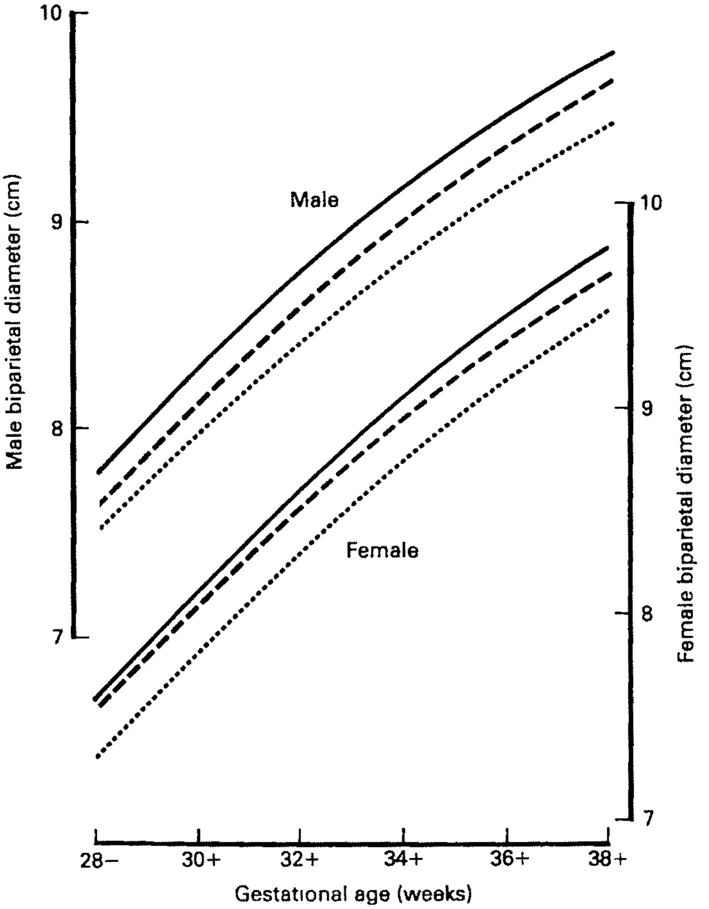

Fig. 1. Mean curves from 28 to 38 weeks gestation for males and females in three birthweight categories: (1) .... 2500–2999 g; (2) ---- 3000–3499 g; (3) ——— 3500–3999 g. Mean (SD) values of the coefficients b_0, b_1 and b_3 for the linear-cubic equations from 13 to 38 weeks gestation in birthweight category (3).

	b_0	b_1	b_3
Male (n=20)	−3·4912	0·4643	$-7{\cdot}8915 \times 10^{-5}$
	(0·9495)	(0·0645)	$(2{\cdot}9242 \times 10^{-5})$
Female (n=14)	−2·7867	0·4176	$-6{\cdot}0413 \times 10^{-5}$
	(0·8878)	(0·0476)	$(1{\cdot}8929 \times 10^{-5})$

Levels of significance (P) between corresponding values of b_0, b_1 and b_3 are 0·036, 0·028 and 0·046 respectively.

gestational ages is similar to that obtained in the cross-sectional analysis. The practice of dating pregnancies by ultrasound fetal BPD measurement at about 16 weeks gestation by assuming that all head sizes are close to a mean value can lead to error because the SDs are such that a fetus whose BPD is 1 SD above the mean at 16 weeks has a value similar to that of a fetus whose BPD is 1 SD below the mean at 18 weeks. The potential for error in age estimation is increased as head size deviates further from the mean. A further source of error in dating pregnancies using this technique may be caused by varying degrees of side-to-side flattening of the fetal head (Sabbagha & Tamura 1983).

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References

Aantaa, K. & Forss, M (1974) Determination of biparietal diameter by the ultrasonic B-scan technique. *Acta Obstet Gynecol Scand* **53,** 121-124.

Campbell, S. (1968) An improved method of fetal cephalometry by ultrasound. *J Obstet Gynaecol Br Commonw* **75,** 568-576

Deter, R. L., Harrist, R. B., Hadlock, F P. & Poindexter, A. N. (1982) Longitudinal studies of fetal growth with the use of dynamic image ultrasonography. *Am J Obstet Gynecol* **143,** 545-554

Flamme, P. (1972) Ultrasonic fetal cephalometry· percentiles curve. *Br Med J* **iii,** 384-385

Jeanty, P., Cousaert, E , Hobbins, J C , Tack, B , Bracken, M. & Cantraine, F. (1984) A longitudinal study of fetal head biometry *Am J Perinatol* **1,** 118-128.

Nyland, T G., Hill, D E., Hendrickx, A. G , Farver, T B , McGahan, J P , Henrickson, R , Anderson, J. & Phillips, H E. (1984) Ultrasonic assessment of fetal growth in the non-human primate *(Macaca mulatta) J Clin Ultrasound* **12,** 387-395.

Pedersen, J. F. (1980) Ultrasound evidence of sexual difference in fetal size in first trimester *Br Med J* **281,** 1253.

Pedersen, J. F. & Mantoni, M. (1985) Difference in fetal size in the first trimester? *Br Med J* **291,** 1278.

Sabbagha, R. E., Barton, F. B & Barton, B. A. (1976) Sonar biparietal diameter. I. Analysis of percentile growth differences in two normal populations using same methodology. *Am J Obstet Gynecol* **126,** 479-484.

Sabbagha, R. E. & Tamura, R K. (1983) Diagnosis of fetal abnormality by ultrasound. In *Recent Advances in Perinatal Medicine* Vol. 1. (Chiswick, M. L., ed.), Churchill Livingstone, London, p 58.

Sebling, A. & McKay, K. (1985) Ultrasound in first trimester shows no difference in fetal size between the sexes. *Br Med J* **290,** 750

University of Manchester Regional Computer Centre (UMRCC) (1980) Statistical Package for the Social Sciences Additional Procedures Vol 1 Regression. pp. 21-43.

Wald, N., Cuckle, H., Nanchahal, K. & Turnbull, A. C. (1986) Sex difference in fetal size early in pregnancy. *Br Med J* **292,** 137.

Wexler, S., Fuchs, C., Golan, A. & David, M. P. (1986) Tolerance intervals for standards in ultrasound measurements Determination of BPD standards. *J Clin Ultrasound* **14,** 243-250.

Wiener, S. N., Flynn, M. J , Kennedy, A W & Bonk, F. (1977) A composite curve of ultrasonic biparietal diameters for estimating gestational age *Radiology* **122,** 781-786

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Alcohol counselling of 85 pregnant problem drinkers: effect on drinking and fetal outcome

ERJA HALMESMÄKI

Summary. Eighty-five pregnant problem drinkers were given intensive counselling throughout gestation to persuade them to reduce or stop their alcohol intake. Nevertheless, 7% of their blood specimens collected at follow-up visits contained ethanol. Fifty-five women (65%) were able to reduce their alcohol consumption by at least 50%. Alcohol abuse was associated in a dose-dependent manner with fetal growth retardation detectable by ultrasonography from 27 weeks gestation. Twenty infants (24%) had a complete fetal alcohol syndrome and 22 (26%) had some features of 'fetal alcohol effects' (FAE). In addition, the rate of structural malformations was high (13%). Of the women with continuous alcohol abuse 89% gave birth to infants with at least one feature of FAE compared with only 40% of those who decreased their alcohol consumption.

It is generally accepted that excessive alcohol ingestion by pregnant women is now the most common teratogen (Jones *et al.* 1973; Clarren & Smith 1978; Streissguth *et al.* 1980). Alcohol abuse during pregnancy also increases the risk of pregnancy complications, such as miscarriage (Harlap & Shiono 1980; Kline *et al.* 1980) and placental abruption (Kaminski *et al.* 1978; Sokol *et al.* 1980). In theory, all these complications are preventable if the pregnant woman could avoid drinking. This paper summarizes the experiences of the efficacy of alcohol counselling and prenatal care given to 85 problem drinkers.

Subjects and methods

In 1983 our hospital opened a special outpatient department for pregnant women with alcohol abuse. In the following 3 years, 85 pregnant women with alcohol abuse were followed and counselled in this department. Twenty-nine patients (34%) had a 5–20 year history of alcohol abuse, and were regarded as 'alcoholics' because they had consumed up to 10–20 alcoholic drinks daily and had several alcohol-related social problems (Table 1). Thirty patients (35%) were regarded as 'heavy drinkers', for, although they had taken between 1 and 10 drinks daily, they had relatively normal social lives, in terms of the family and employment. Twenty-six patients (31%) consumed alcohol only during weekends, but then up to 10 drinks at a time ('moderate drinkers') (Table 1). In addition, 15 patients (18%) used benzodiazepines 1–15 mg daily Six patients had had convulsions after heavy drinking periods before pregnancy, and one of them convulsed twice during pregnancy, although she used carbamazepine 300 mg daily. One patient had had surgery for a semi-malignant ovarian tumour 1 year before pregnancy.

Counselling

After classification of the severity of the alcohol problem at registration, I counselled the patients at 2–4 week intervals about the effects of alcohol (and cigarettes) upon the fetus, and encouraged

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Department of Obstetrics and Gynaecology, University Central Hospital, Helsinki, Finland
ERJA HALMESMAKI *Senior Registrar*

Correspondence: Erja Halmesmaki, MD, Dept. of Obstetrics and Gynaecology, University Central Hospital, Haartmaninkatu 2, 00290, Helsinki, Finland

Table 1. Clinical characteristics of the study population

	Alcoholics (n=29)	Heavy drinkers (n=30)	Moderate drinkers (n=26)
Age (years) mean (SD)	29·2 (4·3)	28·1 (6·0)	27·0 (7·8)
Married	10 (35%)	12 (40%)	10 (38%)
Smokers	21 (72%)	25 (83%)	21 (81%)
Obstetric history:			
One or more previous deliveries	15 (52%)	12 (40%)	12 (46%)
Miscarriage	9 (31%)	6 (20%)	7 (27%)
Pregnancy interruptions	12 (41%)	13 (43%)	13 (50%)

them to abstain totally, or if that was impossible, to decrease their drinking as much as possible. Consultations with social workers and psychiatrists were freely available Furthermore, I encouraged the patients to 'phone the department whenever they liked. Patients who failed to return for follow-up visits were telephoned by me or visited by nurses of local antenatal centres, with the aim of persuading them to come to the department.

At each visit to the department the following variables were routinely studied: symphysis–fundus height, cervical status, blood pressure, protein and glucose in urine, gas chromatographic analysis of blood and/or urine for ethanol, fetal ultrasonography and cardiotocography. The duration of gestation was estimated from the detailed menstrual history and from ultrasound findings before 23 weeks gestation. The treatment was free of charge to the patients.

The infants were examined at age 5 days and at 4, 6, and 12 months The criteria for 'fetal alcohol effects' (FAE) were the presence of at least one of the following characteristics: growth retardation (low birthweight, short length and small head circumference; all below the normal 10th centile at birth or below the mean −2 SD at follow-up visits), distinctive facial features (low nasal bridge and short upturned nose short palpebral fissures, indistinct philtrum, thin upper lip) or neurological aberrations and/or developmental delay (Jones *et al.* 1973; Clarren & Smith 1978; Streissguth *et al.* 1980). The criteria of fetal alcohol syndrome (FAS) were fulfilled if the infant showed growth retardation, distinctive facial features, neurological aberrations and/or developmental delay (Rosett *et al.* 1981)

The significance of the differences in the mean values and percentages were tested by analysis of variance and binomial test, respectively.

Results

Thirty-six patients registered between 12 and 20 weeks gestation and 39 patients between 21 and 32 weeks. Of the 36 women booked between 12 and 20 weeks 94% reduced their drinking by at least 50% compared with only 54% of those who booked later ($P<0·0005$, binomial test). None of the 10 patients counselled for the first time after 32 weeks gestation could reduce alcohol use Taken together, 55 patients (65%) reduced their drinking by at least 50% after registration at the department (Fig. 1).

Ethanol at concentrations from 0·5 mmol/l to 73·3 mmol/l (22·4 mmol/l = 100 mg/dl) was detected in 27 of 376 blood samples (7%) taken at the visits to the department. Two patients presented twice and one patient four times with ethanol in the blood. Ethanol was also found in 21 of 349 urine samples (6%) with a concentration range between 0·2 and 55·0 nmol/l.

Ultrasonographic scanning revealed an association between fetal growth retardation and maternal alcohol abuse from 27 weeks gestation onwards (Fig. 2). No fetal cardiotocographic patterns characteristic of maternal alcohol abuse could be identified.

Placental abruption occurred in four women (5%) who were delivered by caesarean section, and the infants survived. The mean birthweight in alcoholics, 2740 (SD 441) g, was less ($P<0·05$, analysis of variance) than that in heavy drinkers, 3232 (SD 684) g, and moderate drinkers, 3403 (SD 294) g (Table 2).

All infants were examined at age 5 days, 72 infants also at 4–6 months and 47 at 12 months. In nine infants, no follow-up could be done due to maternal reluctance. Fetal alcohol effects were seen in 42 infants, of whom 20 had a full-blown FAS (20/85 = 24%) (Fig. 1) Nine of the alcohol-damaged infants and two others (11/85 = 13%) had structural malformations (Table 3). The occurrence of malformations did not correlate with intake of benzodiazepines. Five of the infants in the study (6%) have died (one stillborn with multiple anomalies, one with hypoplastic

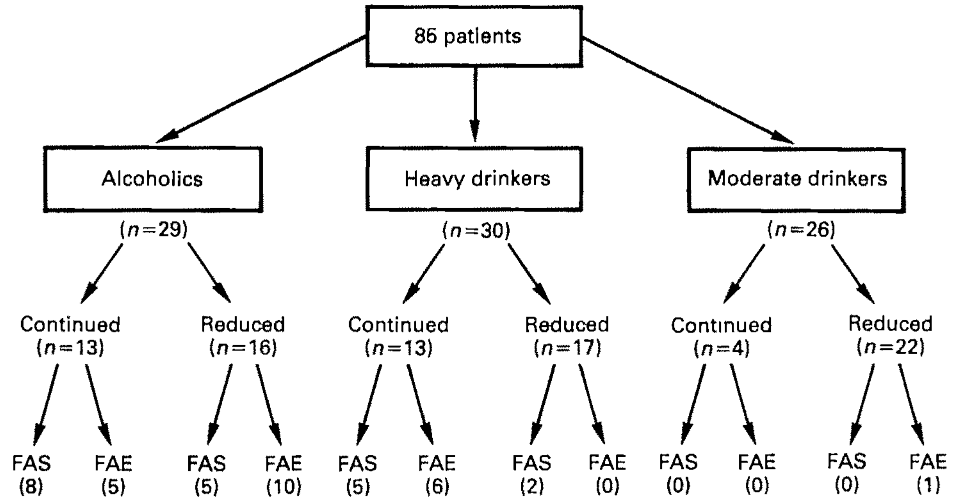

Fig. 1. Effect of counselling on maternal alcohol consumption and frequency of fetal damage. FAS, Fetal alcohol syndrome; FAE, fetal alcohol effect.

left ventricle died aged 6 h, one died because of respiratory distress syndrome, one sudden infant death at 14 days, and one traumatic death at 1·5 years). The perinatal and neonatal mortality rates were 2·4% and 4·7%, respectively.

The frequency of FAS and FAE was related to maternal drinking during pregnancy (Table 3). Fetal damage developed in 24 infants (89%) of patients with no decrease in their alcohol consumption during pregnancy, but only in 18 infants (40%) if the patient reduced her drinking during pregnancy (Table 3).

Discussion

Alcohol abusers are seldom responsive to health education spread by mass media (Pittman 1980), and pregnant women are no exception to this rule. Therefore, intensive alcohol counselling was given as part of the prenatal care of women

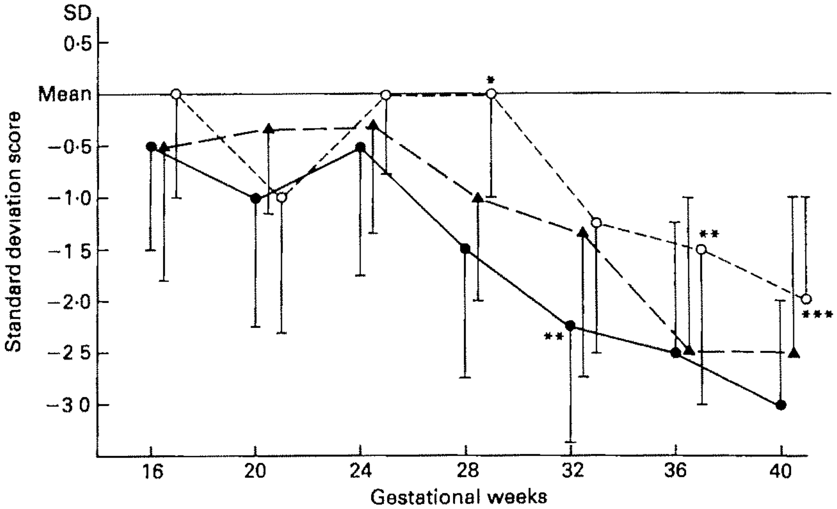

Fig. 2. Fetal biparietal diameters (mean ± SD) in alcoholics (●), in heavily (▲), and in moderately drinking (○) patients. The line of mean and standard deviation scores are derived from 15 000 normal pregnancies studied in the same hospital (Aantaa & Forss 1980). Significance of difference compared with other groups: *$P<0·0025$; **$P<0·025$ compared with alcoholics; ***$P<0·05$ (analysis of variance)

Table 2. Perinatal variables in relation to maternal alcohol abuse (analysis of variance)

	Alcoholics ($n=29$)	Heavy drinkers ($n=30$)	Moderate drinkers ($n=26$)	Total ($n=85$)
Maternal weight gain during pregnancy (kg) mean (SD)	7·9 (5·8)*	10·9 (5·2)	13·2 (3·5)	11·0 (4·9)
Placental abruption	1 (36 weeks)	2 (33 and 37 weeks)	1 (36 weeks)	4 (5%)
Birthweight (g) mean (SD)	2740 (441)*	3232 (684)	3403 (294)	3136 (606)
Infants with IUGR	26 (90%)**	10 (33%)	4 (15%)	40 (47%)
Placental weight (g) mean (SD)	518 (117)***	577 (125)	646 (64)	592 (101)

*$P<0{\cdot}05$ when compared with heavy and moderate drinkers; **$P<0{\cdot}0005$ when compared with heavy and moderate drinkers; ***$P<0{\cdot}05$ when compared with moderate drinkers.
IUGR, Intrauterine growth retardation.

with alcohol abuse in the present study. For ethical reasons, all alcohol abusers must be given the same counselling and treatment and it was impossible to form a non-counselled control group. Moreover, with increasing knowledge of FAE and FAS (Jones *et al.* 1973; Ouellette *et al.* 1977; Clarren & Smith 1978; Streissguth *et al.* 1980; Halliday *et al.* 1982), these syndromes are recognized today more easily than some 10 years ago and it is impossible to obtain a reliable retrospective control group. Thus, the efficacy of alcohol counselling in reducing fetal risks cannot be studied in 'controlled' trials. The teratogenicity of alcohol is, however, strictly dose dependent (Streissguth *et al.* 1980) and any reduction of alcohol use must improve fetal chances.

In the present study, 65% succeeded in reducing their drinking, apparently as a result of information and/or psychological support received during repeated counselling sessions. This conclusion is supported by the fact that the longer patients took part in counselling, the more effective it was. However, I cannot exclude with certainty the possibility that patients who registered early were likely to reduce their drinking even without counselling, a problem also present in other studies of alcohol counselling of pregnant women (Larsson 1983; Rosett *et al.* 1983).

Ethanol was undetectable in 93–94% of blood and urine samples. This implies that the majority of patients could refrain from alcohol for at least 10–12 h before the sessions, but it does not prove any longer abstinence. The percentage seems,

Table 3. Neonatal findings in relation to maternal alcohol use

	Women with continued alcohol abuse ($n=30$)	Women with reduced drinking ($n=55$)
Infants at follow-up (n)	27	45
FAS	13 (48%)	7 (16%)
FAE	11 (41%)	11 (24%)
Healthy infants	3 (11%)	27 (60%)
Characteristics:		
Weight and height < mean −2 SD	14 (52%)	8 (18%)
Head circumference < mean −2 SD	19 (70%)	5 (11%)
Neurological aberrations	22 (81%)	20 (44%)
Distinctive facial features	24 (89%)	15 (33%)
Malformations:	4 (13%)	7 (13%)
Polydactylia	1	1
Talipes		3
Multiple limb anomaly*		1
Oesophageal atresia		1
Cardiac murmur (ASD or VSD†)	3	
Hypoplastic left ventricle	0	1

*Distal phalanges missing in six fingers, bilateral talipes and two missing toes, stillborn at 31 weeks.
†Atrial or ventricular septal defect.
FAS, Fetal alcohol syndrome; FAE, fetal alcohol effects.

however, surprisingly high in view of the drinking histories of the patients, and it may thus support the usefulness of the treatment.

Fetal growth retardation is one of the most reliable features of FAE, yet it has remained unknown at which phase of gestation alcohol abuse can cause this effect. The present data show that alcohol dose-dependent intrauterine growth retardation (IUGR) can be detected ultrasonically from 27 weeks gestation; but they cannot directly indicate whether IUGR can be modified if the woman reduced or stopped drinking, although in view of the dose dependence of IUGR this possibility seems likely.

The rates of FAS and FAE were significantly reduced among the women who decreased their drinking. This finding is supported by previous data showing that the most severely damaged infants are born to women with continuous alcohol abuse (Streissguth *et al.* 1980; Wright & Toplis 1986). Therefore, all efforts should be focused on alcohol withdrawal from pregnant problem drinkers, and antenatal clinic staff should be educated to identify alcohol abusers, counsel them, and give them psychological support to refrain from alcohol.

Infants born to drinkers commonly show a number of malformations (Jones *et al.* 1973; Clarren & Smith 1978; Halliday *et al.* 1982). In this series, the anomalies, with one exception, affected predominantly the heart and limbs, and their rate was not reduced among those who decreased their drinking. This may be explained by the fact that reduction in alcohol consumption took place only after morphogenesis, and elimination of such abnormalities would require intervention very early in pregnancy.

In conclusion, two of three pregnant alcohol abusers could significantly reduce their use of alcohol with the help of a special treatment programme, and this decreased the risk of fetal damage from 89% to 40%. Therefore, alcohol abuse during pregnancy should be recognized as early as possible and counselling should be given to reduce fetal risks.

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References

Aantaa, K. & Forss, M (1980) Growth of the fetal biparietal diameter in different types of pregnancies. *Radiology* **137**, 167-169

Clarren, S. K & Smith, D W. (1978) The fetal alcohol syndrome. *N Engl J Med* **298**, 1063-1067.

Halliday, H. L., Reid, M. McC. & McClure, G. (1982) Results of heavy drinking in pregnancy *Br J Obstet Gynaecol* **89**, 892-895.

Harlap, S. & Shiono, P. H (1980) Alcohol, smoking and incidence of spontaneous abortions in the first and second trimester. *Lancet* **ii**, 173-176.

Jones, K L , Smith, D. W., Ulleland, C. N. & Streissguth, A. P. (1973) Pattern of malformation in offspring of chronic alcoholic mothers. *Lancet* **i**, 1267-1271.

Kaminski, M., Rumeau-Rouquette, C & Schwartz, D. (1978) Alcohol consumption in pregnant women and the outcome of pregnancy. *Alcoholism Clin Exp Res* **2**, 155-163

Kline, J., Stein, Z A , Shrout, P., Susser, M. & Warburton, D. (1980) Drinking during pregnancy and spontaneous abortion. *Lancet* **ii**, 176-180.

Larsson, G. (1983) Prevention of fetal alcohol effects An antenatal program for early detection of pregnancies at risk. *Acta Obstet Gynecol Scand* **62**, 171-178

Ouellette, E. M., Rosett, H. L , Rosman, N P. & Weiner, L (1977) Adverse effects on offspring of maternal alcohol use during pregnancy *N Engl J Med* **297**, 528-530.

Pittman, D. J. (1980) Primary prevention of alcohol abuse· five models of social control. In *Primary Prevention of Alcohol Abuse and Alcoholism.* St Louis, Social Science Institute, Washington University, pp 11-16.

Rosett, H. L., Weiner, L. & Edelin, K C. (1981) Strategies for prevention of fetal alcohol effects. *Obstet Gynecol* **57**, 1-7

Rosett, H. L , Weiner, L & Edelin, K C (1983) Treatment experience with pregnant problem drinkers. *JAMA* **249**, 2029-2033.

Sokol, R. J , Miller, S. I & Reed, G (1980) Alcohol abuse during pregnancy: an epidemiological model. *Alcoholism Clin Exp Res* **4**, 135-145

Streissguth, A P , Landesman-Dwyer, S., Martin, J. C. & Smith, D W. (1980) Teratogenic effects of alcohol in human and laboratory animals *Science* **209**, 353-361.

Wright, J T & Toplis, P. J (1986) Alcohol in pregnancy. *Br J Obstet Gynaecol* **93**, 201-202.

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References ranges and sources of variation for indices of pulsed Doppler flow velocity waveforms from the uteroplacental and fetal circulation

J. M. PEARCE, S. CAMPBELL, T. COHEN-OVERBEEK, G. HACKETT, J. HERNANDEZ, J. P. ROYSTON

Summary. Variation in indices used to characterize the maximum frequency outline of waveforms obtained from the uteroplacental and fetal circulations by duplex Doppler ultrasound was studied between observers, over a 24-h period and before and after a meal. No significant differences were found. Reference ranges were derived for three indices, the A/B ratio, the resistance index and the pulsatility index, for waveforms from the fetal descending aorta, umbilical artery, and the placental and maternal sides of the uteroplacental circulation. Indices from waveforms from the uteroplacental circulation demonstrated a fall from 16 to 24 weeks gestation with no change thereafter. The umbilical artery indices demonstrated a continuing fall with increasing gestation but the A/B ratio and resistance index from the fetal descending aorta did not change with gestation. The pulsatility index from the aorta demonstrated a gentle rise.

The ability to interrogate the fetal and uteroplacental circulation by means of Doppler ultrasound has clinical potential. Initial studies on the fetal circulation involved estimation of volume flow and/or peak velocity in the umbilical vein (Gill *et al.* 1981) and the descending fetal aorta (Eik-Nes *et al.* 1980; Griffin *et al* 1984). Methodological problems involved in measuring vessel diameter and in determining the angle of insonation led to large errors in quantitive volume estimations (Griffin *et al.* 1983; Eik-Nes *et al.* 1984). Interest has therefore turned to indices which measure flow impedance rather than volume flow; these are derived from the maximum velocity envelope of such waveforms. This is especially so in the uteroplacental circulation where the vessels are of small and varying diameter (2–4 mm) and quantification of flow into the intervillous space is impractical. In order to use indices which characterize the maximum frequency outline of the waveform in clinical management, it is important to establish reference ranges throughout pregnancy and to determine the natural sources of variation. This paper sets out to fulfil these requirements.

Patients and methods

The details of the duplex pulsed Doppler system have been described previously (Griffin *et al.* 1983, 1984). With the patient in the semi-recum-

Department of Obstetrics and Gynaecology, King's College Hospital, London
J. M. PEARCE
S. CAMPBELL
T. COHEN-OVERBEEK
G. HACKETT
J. HERNANDEZ

Division of Medical Statistics, Clinical Research Centre, Northwick Park Hospital, London
J. P. ROYSTON

Correspondence: J M. Pearce, Department of Obstetrics and Gynaecology, St George's Hospital Medical School, Cranmer Terrace, London SW17 0RE

bent position or with a 10° left lateral tilt the fetal descending aorta was located with the real-time transducer of the duplex system. The range gate of the pulsed Doppler beam was placed over the vessel and the sample volume adjusted until it extended just beyond the limits of the vessel. Minor adjustments to the beam were made until the audible signal and the visual waveform were considered ideal (Griffin *et al.* 1983). At least 10 waveforms were recorded and stored on audio tape for later analysis. A portion of the umbilical cord was then displayed and the Doppler beam was adjusted until an ideal signal was obtained simultaneously from both the umbilical artery and vein. Again at least 10 waveforms were recorded for later analysis.

Recordings from both these vessels were made during periods of fetal apnoea. Fetal breathing movements are known to have marked effects on fetal blood flow (Marsal *et al.* 1984). Breathing movements at the time of the umbilical artery recordings were easily recognized by fluctuations in the normal steady state, continuous flow in the umbilical vein. Breathing movements during the course of recording the signals from the fetal aorta were recognized most readily by alterations in the aortic sonogram together with obvious movements of the fetal chest wall.

Waveforms from the uteroplacental circulation were obtained by imaging the myometrium to locate a vessel of 2–4 mm in diameter running towards the placenta. As the Doppler-shifted signal from these vessels is of relatively low frequency it was nearly always possible to interrogate the vessel with the pulse repetition rate at the lower setting (2·5 kHz). This allowed simultaneous recording of the Doppler signals with real-time viewing of the vessel. Again 10 cardiac cycles were recorded on audio tape for later analysis.

If such a vessel could not be seen then the external iliac artery with its characteristic triphasic waveform was located and the myometrium suprolateral to this point was searched blind until the characteristic flow velocity waveform was obtained. Before recording the signal care was taken to ensure that the range gate was well below the abdominal wall so that recordings were not made from anterior abdominal wall vessels. A vessel on the side of the uterus furthest away from the placental site was then sought and recorded in a similar fashion.

The flow velocity waveforms were recorded with the vessel wall (high pass) filter set at 150 Hz. The power output from the Kranzbeuhler duplex pulsed Doppler system at low pulse repetition frequencies (2·5 kHz) is 43 mW with a spatial peak, temporal average of 112 W/cm^2.

The height of the maximum frequency outline of the flow velocity waveform is dependent upon the angle subtended between the Doppler beam and the vessel being examined (the angle of insonation). The greater the angle the lower the frequency recorded in the waveform. To allow direct comparison of flow velocity waveforms, four ratios have been described which relate one part of the waveform to another (Fig. 1). The frequency index profile (Campbell *et al.* 1983) allows the waveform to be redrawn after it has been normalized for the angle of insonation. This was achieved initially by determining the maximum frequency of the waveform at equal intervals along the waveform and then dividing the obtained frequency by the sum of the frequencies. The frequency index profile was introduced to allow the recognition of subtle changes within the waveform which were not reflected in the other indices that characterize waveforms.

All indices are dependent upon the length of the cardiac cycle, in that the longer the cycle the better the chance of obtaining lower or absent frequencies in end-diastole. This can be overcome if the waveform is divided by a set number of points (e.g. 256) rather than equal divisions. The use of a computer program has made this task relatively accurate and simple. All ratios subsequently used in this paper were derived after the waveform had been normalized and standardized for the length of the cardiac cycle. Summary statistics for the frequency index profile are, however, complex and study of sources of variation is not practical.

Method of analysis of flow velocity waveforms

The recorded waveforms were played back through a spectrum analyser (Doptec Ltd, Chichester, UK). Of the 10 recorded waveforms the best three were used for analysis. These were chosen as being free of noise and with a clear maximum frequency outline. The waveform was displayed on the screen of a BBC model B computer (Acorn Ltd, Cambridge, UK) by a videodigitizer (RH Electronics, Cambridge, UK). This allowed the maximum outline of the flow velocity waveform from a single cardiac cycle to

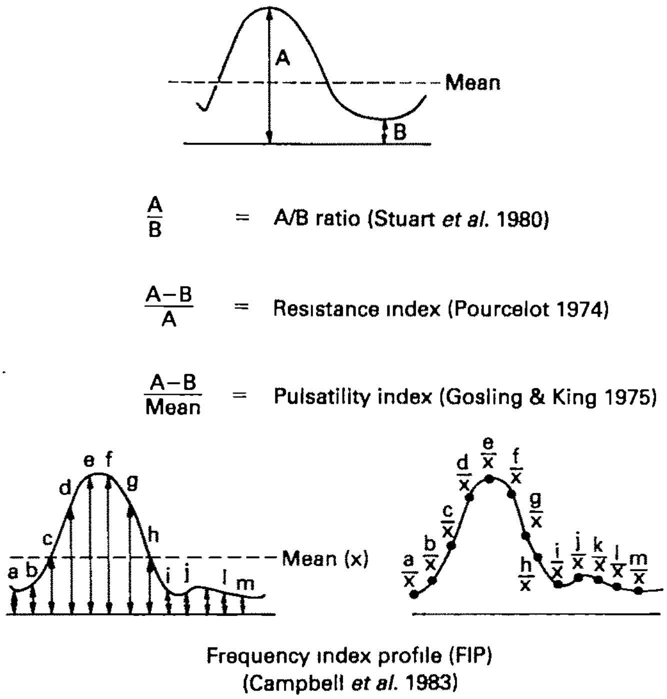
A
B
Mean
A/B = A/B ratio (Stuart et al. 1980)
(A−B)/A = Resistance index (Pourcelot 1974)
(A−B)/Mean = Pulsatility index (Gosling & King 1975)
a b c d e f g h i j l m
Mean (x)
a/x b/x c/x d/x e/x f/x g/x h/x i/x j/x k/x l/x m/x
Frequency index profile (FIP)
(Campbell et al. 1983)

Fig. 1. Indices used to characterize the maximum frequency outline of flow velocity waveforms.

be traced and divided into 256 equal parts. This number was chosen as it was convenient for the computer's memory system. Each point was divided by the mean of all 256 values and the normalized waveform was then drawn. The resultant waveform known as the frequency index profile is then independent of both the angle of insonation and the length of the cardiac cycle (heart rate). The A/B ratio, the resistance index (RI) and the pulsatility index (PI) were then averaged over three such normalized waveforms.

Reference ranges

To determine the reference range for each of the indices, 40 patients were recruited and studied longitudinally every 4 weeks from 16–18 weeks gestation until delivery. Patients with no previous obstetric complications and no apparent medical problems were approached at the time of their first visit to the antenatal clinic. Any patient who developed a complication of pregnancy was subsequently withdrawn from the study.

Longitudinal studies were considered necessary as it was envisaged that the reference ranges would be used to study changes in individual patients with increasing gestation as well as to evaluate isolated measurements. All patients had their gestation confirmed by ultrasound on recruitment to the study (Warsof *et al.* 1983).

Sources of variation

Variation between observers and within patients was studied as follows. Three observers independently recorded flow velocity waveforms from 10 women in the last trimester of an uncomplicated pregnancy. Ten waveforms were obtained from each of the following vessels: fetal aorta, umbilical artery, the placental and non-placental arcuate artery. These waveforms were stored on audio tape for subsequent analysis.

Diurnal variation was studied in 10 women in the third trimester of an apparently uncomplicated pregnancy. Each woman was studied every 4 h by one observer (J.M.P.). Five were studied from midnight to 20.00 hours and the other five from 22.00 to 18.00 hours. In addition, to assess the effects of eating a meal, five women were studied 30 min before and 1 h after they had eaten hospital lunch.

Statistical methods

Reference ranges

Each index was plotted against week of gestation and was logarithmically transformed before further analysis if skewness was present. Reference ranges were constructed by regressing each index on gestational age and calculating intervals around the fitted line that contained an estimated 90% and 95% of the values. However, since the data were longitudinal and therefore not independent, analysis of covariance (Baker & Nelder 1985) was used to detect interaction (non-parallelism) between individual regression lines and different patient intercepts. Quadratic or linear terms were included only if their regression coefficients were significantly different from zero at the 5% level. Providing that parallelism was present, a single regression line and its residual standard deviation was accepted as an adequate description of the data for the purposes of calculating the reference ranges.

Outliers were dealt with as follows. Patients and waveforms that generated discordant values (resulting in large residuals in the above analysis) were examined again for incorrect data. All apparently valid data were analysed again by robust regression (Mosteller & Tukey 1977).

Sources of variation

Sources of variation were examined by two-way analysis of variance. Homogeneity of variance was examined by means of Bartlett's test and the normal plot of residuals by the Shapiro–Francia *W*-test (Royston 1983) using the computer package SPP (J. P. Royston 1984, privately released). In the observer variation study, observers and patients were considered as random effects, but in the study of variation with the time of day, time was considered as a fixed effect. Coefficients of variation between observers were then derived from the analysis of variance tables. Differences in mean waveform indices (from 10 waveforms) before and after meals were assessed by means of a paired *t*-test.

Table 1. Coefficients of variation (%) for diurnal variation of waveforms

	A/B ratio	RI	PI
Umbilical artery	6·0	4·5	7·0
Aorta	3·5	1·0	4·6
Placental arcuate artery	4·7	4·5	11·0
Non-placental arcuate artery	7·3	5·4	12·0

RI, Resistance index; PI, pulsatility index.

Results

Diurnal variation and the effect of a meal

No significant difference between times over the 24-h period was observed in any of the indices in any of the vessels from the 10 patients. The coefficients of variation are shown in Table 1. No significant differences were found for any of the indices from any of the vessels between before and after meals (Table 2).

Observer variation

No significant differences were observed for any of the indices between the measurements made by the three different observers (Table 3). The maximum coefficient of variation was observed in the A/B ratio of the aorta and was 12·6%.

References ranges

Of the original 40 women recruited, six either developed some complication of pregnancy, left the district or refused to continue with the testing so that data for 34 patients were available for analysis. Details of these patients are shown in Table 4.

Table 5 gives the regression formulae for each of the indices. Of the 12 variables analysed, 10 required log transformation and six showed curvature against gestational age and were best approximated by quadratic models. There was no significant change with gestational age for the A/B ratio and the RI of the aortic waveforms; however, the PI increased with increasing gestation. This contrasted with the findings from the umbilical artery where the mean value of all three indices fell with increasing gestational age. Outliers which could not be ascribed to gross errors were few, and occurred almost exclusively in waveforms obtained before 20 weeks gestation.

The scatter plot for the RI of the arcuate artery together with the fitted regression line and reference ranges are shown in Figs 2 and 3. All indices from the arcuate arteries showed a fall

Table 2. Effect of meals on indices characterizing waveforms

	A/B ratio	RI	PI
Umbilical artery			
Before meals	2·24 (0·47)	0·53 (0·08)	0·77 (0 20)
After meals	2·25 (0·45)	0·53 (0·10)	0·78 (0·23)
Aorta			
Before meals	5·65 (1·54)	0·81 (0·06)	1·73 (0·26)
After meals	5·66 (1·67)	0·81 (0·07)	1·73 (0·27)
Placental arcuate artery			
Before meals	1·56 (0·25)	0·41 (0·16)	0·49 (0·19)
After meals	1·52 (0·26)	0·43 (0·13)	0·50 (0·17)
Non-placental arcuate artery			
Before meals	2·01 (0·77)	0·46 (0·14)	0·68 (0·35)
After meals	2·05 (0·84)	0·46 (0·13)	0·60 (0·18)

Results are means (SD). None of the above changes was significant at the 5% level.
RI, Resistance index; PI, pulsatility index.

until 24 weeks gestation and no change thereafter.

Discussion

Observer and diurnal variation

None of the indices obtained from any of the sites showed a significant variation within or between observers or during the course of a day. Furthermore, no apparent difference was observed in the waveforms before or after meals. This indicates that it is not necessary to standardize the timing of Doppler examinations diurnally or in relation to meals. Furthermore, results obtained by different observers should show very small variations.

Reference ranges

As yet there is no universally used index for assessing blood flow impedance in the uterine and fetal vessels. The PI is the only index that can be used when there is absence of end-diastolic flow or reverse flow. Many workers, however, use the A/B ratio or RI and we have

Table 3. Observer variation between 10 patients

	A/B ratio	RI	PI
Umbilical artery			
Observer 1	3·95 (1 13)	0·73 (0·09)	1·23 (0·29)
2	3·84 (1·11)	0·69 (0·09)	1·19 (0·21)
3	4·12 (0·92)	0 78 (0·08)	1·32 (0·19)
Aorta			
Observer 1	9·32 (2·45)	0·88 (0·03)	2·16 (0·32)
2	10·35 (2 97)	0·89 (0·04)	2·30 (0 33)
3	11·49 (1·38)	0·91 (0·02)	2·37 (0·26)
Placental arcuate artery			
Observer 1	2·12 (0·76)	0·48 (0·06)	0·76 (0·05)
2	2·03 (0·68)	0·42 (0·16)	0·66 (0·05)
3	1·75 (0·54)	0·40 (0·11)	0·52 (0·04)
Non-placental arcuate artery			
Observer 1	2·23 (0·94)	0·49 (0·18)	0·73 (0·39)
2	2·30 (1·25)	0·61 (0·17)	1·04 (0·54)
3	2 35 (1·17)	0·57 (0·18)	0·87 (0·55)

Results are means (SD) values. There were no significant differences between the three observers for any of the indices
RI, Resistance index; PI, pulsatility index.

Table 4. Characteristics of the 34 patients used in the construction of the reference ranges

Characteristic	*n* (%)	Mean (SD)	Range
Age (years)		26·0 (5·6)	18– 35
Height (cm)		156·8 (27·8)	149–175
Weight (kg)		58·8 (6·8)	49– 77
Primigravidae	21 (68)		
Married	21 (62)		
Race			
White	21 (62)		
Black	10 (29)		
Asian	3 (9)		
Cigarette smokers	3 (9)		
Gestation at delivery (weeks)		40·3 (1·3)	37·5–42·3
Mode of delivery			
SVD	23 (68)		
FD	5 (15)		
LSCS	6 (17)		
fetal distress	1		
failure to progress	3		
breech	2		
Birthweight (kg)		3·38 (0·29)	2·8–4·1
Males	17 (50)		
Apgar scores			
<6 at 1 min	1 (3)		
<6 at 5 min	0		

SVD, Spontaneous vaginal delivery; FD, forceps delivery; LSCS, lower segment caesarean section.

therefore included them in this study. It should be noted, however, that the A/B ratio and the RI are effectively the same since

$$\text{RI} = 1-1/(\text{A/B}).$$

Analysis of longitudinal data defeats the assumption of independence necessary for regression analysis. Use of analysis of covariance regresses data for each individual patient on gestational age and then compares both the slopes and the intercepts. For each index measured the regression lines from each

Table 5. Regression formulae for flow velocity waveforms

Index	Tsn	Const.	Lin. ($\times10^{-3}$)	Quad. ($\times10^{-3}$)	Res. SD	Outliers
Umbilical artery						
A/B ratio	$\log_e$	1·175	8·40	−0·504	0·188	2
RI	none	0·652	6·25	−0·247	0·061	0
PI	$\log_e$	0·585	−22·89	—	0·150	0
Aorta						
A/B ratio	$\log_e$	1·708	—	—	0·256	
RI	none	0·812	—	—	0·049	3
PI	$\log_e$	0·327	6·40	—	0·114	3
Placental arcuate artery						
A/B ratio	$\log_e$	0·994	−29·55	0·392	0·107	3
RI	$\log_e$	−0·240	−41·57	0·546	0·180	2
PI	$\log_e$	0·352	−61·38	0·831	0·242	4
Non-placental arcuate artery						
A/B ratio	$\log_e$	1·172	−34·32	0·415	0·171	4
RI	$\log_e$	−0·454	−15·00	—	0·220	1
PI	$\log_e$	0·032	−21·16	—	0·321	4

Tsn, Transformation; Const., constant; Lin., linear coefficient; Quad , quadratic coefficient; Res SD, residual standard deviation.

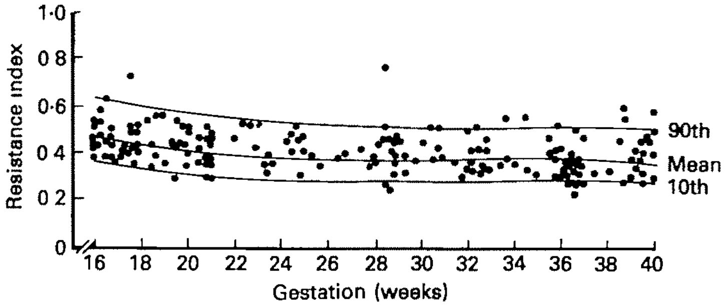

Fig. 2. Regression line and reference range for the resistance index from an arcuate artery on the placental side Log$_e y = -0{\cdot}24 - 41{\cdot}57 \times 10^{-3}x + 0{\cdot}55 \times 10^{3}x^{2}$.

patient were parallel. This allowed the data to be summarized by means of a single regression line together with residual standard deviation (SD), from which references ranges were calculated as fitted value ±1·65 (90% range) or ±1 96 (95% range) times the residual SD.

Examination of the regression lines of all indices from the arcuate artery on the placental side of the uterus demonstrates a fall with increasing gestation until approximately 24 weeks (Fig. 2). Thereafter, there appears to be little or no change with gestational age. We have previously speculated that the cause of this fall may be due to trophoblastic invasion of the spiral arteries (Campbell *et al.* 1983). Brosens *et al.* (1967) have demonstrated that trophoblastic invasion in normal pregnancies is complete by about 22 weeks gestation. The invasion results in the spiral arteries being deprived of their muscular coat throughout their entire length. As the sonograms are recorded from an artery that is proximal to the spiral arteries such a fall in the peripheral resistance should result in an increase in the height of frequencies recorded in end-diastole (Olsen & Cooke 1975). The fall in all three indices used to characterize the waveforms from the placental side of the uterus is due largely to increase in height in end-diastolic frequencies.

Such a change is not readily seen by study of the regression lines obtained from the non-placental side of the uterus (Fig. 3). These lines show a continuing fall with increasing gestation for all three indices with increasing gestation. Analysis of outlying points (above the 95% range) showed that they were largely due to three patients. Review of the pregnancies of these three patients failed to indicate any difference from the remaining 31 patients and in addition the values for the indices of the flow velocity waveforms obtained from the placental side of the uterus are well within the 90% range. In all three patients the placenta was clearly seen not to cross the midline of the uterus. Interpretation of the non-placental arcuate waveforms must be done in conjunction with accurate placental location.

Trudinger *et al.* (1985) have published the only other reference range for indices from the uteroplacental circulation. They produced their range

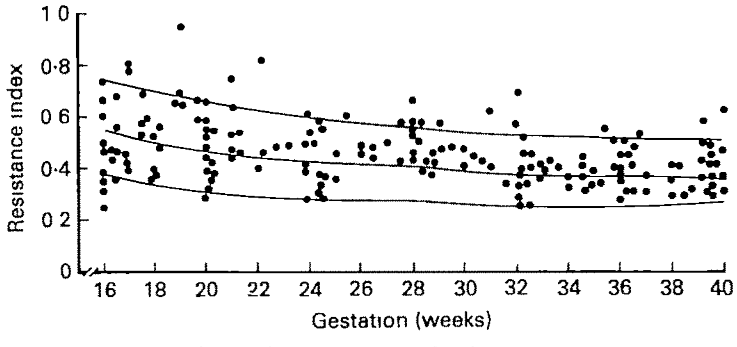

Fig. 3. Regression line and reference range for the resistance index from an arcuate artery on the non-placental side. Log$_e y = -0\ 45 - 15{\cdot}00x$

from 12 normal patients and used an index of least diastolic to maximum systolic frequency (the inverse of the A/B ratio). They demonstrated a continuing fall in this index and suggested that this was due to progressive increase in the cross-sectional area of the uterine vascular bed as observed in ovine pregnancy. It is difficult to compare our data with those reported by Trudinger *et al.* (1985) because they used continuous Doppler and although the placental bed was located initially by real-time ultrasound it is impossible to be certain about the source of the signal in the absence of a range gate. Furthermore, they made no correction for the increase in maternal heart rate which occurs with increasing gestation (Hytten & Leitch 1971).

The finding that all the indices characterizing the umbilical artery waveforms fall with increasing gestation indicates that the fetal/placental circulation expands throughout pregnancy. Our ranges for the umbilical artery are consistently lower than those published previously, most of which were derived by continuous wave Doppler ultrasound. Trudinger *et al.* (1985) studied 12 patients from 28 weeks gestation and although their reference range fits within our reference range, our mean values are lower by approximately 1 SD. The ranges published by Stuart *et al.* (1980) and Fitzgerald *et al.* (1984) for the A/B ratio also fit within our reference range but again our mean values are lower.

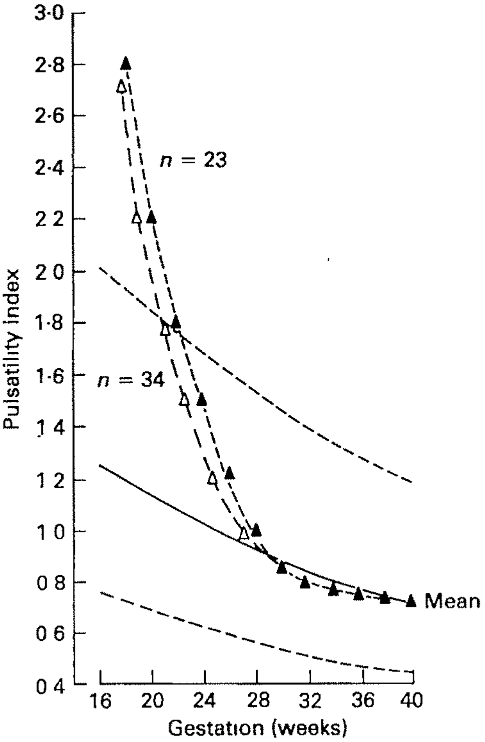

Fig. 4. The pulsatility index from the umbilical artery The regression line from the present study before (△— · △) and after (——) correction for fetal heart rate is demonstrated. ▲– – –▲, The regression line derived from Reuwer *et al.* (1984) and references ranges (– – – –) after corrected for heart rate are also shown

Furthermore, we did not see the large fall in the A/B ratio observed by Stuart *et al.* (1980) from 16 to 24 weeks gestation. This large initial fall has also been noted by Reuwer *et al.* (1984) in their reference range for the PI derived from pulsed Doppler studies; this was almost identical with the findings in the present study if no correction is made for fetal heart rate (Fig. 4). Even with this correction there is coincidence of the means with those of Reuwer *et al.* (1984) from 28 weeks gestation onwards.

We believe that our references ranges are generally lower than other published data because we have included a correction for heart rate before deriving the indices. The fetal heart rate falls with increasing gestation (Fig. 5). This fall is greatest from 16 to 18 weeks and is small from 28 weeks to term. Corrections for heart rate would therefore tend to lower the references range and would be most marked in early pregnancy. This seems to account for the differences. We believe this correction for heart rate should be retained as the indices are believed to reflect the placental resistance (Giles *et al.* 1985) and standardizing for fetal heart rate allows the changes in downstream impedance in the villous circulation that occur with increasing gestation to be more accurately assessed. Furthermore, if Doppler ultrasound is to be used to study the effects of drugs or exercise on the placental or fetal circulation then standardization for heart rate is a necessary preliminary.

Reference ranges for the aorta have been published only for the third trimester. Griffin *et al.* (1984) found no significant changes for any of the indices with increasing gestation throughout the third trimester. We would concur with the observation on the A/B ratio and the RI and furthermore we found no significant changes in these indices from 16 weeks to term. Moreover, the mean values from the present study (A/B ratio, 5·93; RI, 0·81) do not differ from those reported by Griffin *et al.* (1983) (A/B ratio, 6·2;

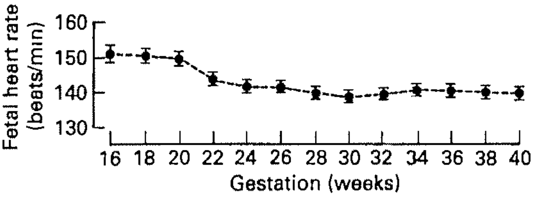

Fig. 5. The change in fetal heart rate with gestation. Ī, Mean ±2 SE.

RI, 0·82). However, the PI from the aorta showed a slight but significant increase with increasing gestation which could be due to decreasing vessel compliance or increasing peripheral resistance within the fetus from renal and mesenteric arteries and from the limb arteries. If the latter is true then the rise in peripheral resistance would need to be substantial as the flow velocity waveform from the umbilical artery suggests decreasing placental resistance with increasing gestation.

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References

Baker, R. J. & Nelder, J A. (1985) *GLIM system, release 3.77.* Numerical Algorithms Group, Oxford

Brosens, I., Robertson, W. B. & Dixon, H. G (1967) The physiological response of the vessels of the placental bed to normal pregnancy. *J Path Bact* **93**, 569-574.

Campbell, S., Diaz-Recasens, J., Griffin, D. R., Cohen-Overbeek, T. E , Pearce, J. M., Willson, K. & Teague, M J. (1983) New Doppler technique for assessing uteroplacental bloodflow *Lancet* **i**, 675-677.

Eik-Nes, S. H., Brubakk, A. O. & Ulstein, M (1980) Measurement of human fetal blood flow. *Br Med J* **280**, 283-284.

Eik-Nes, S. H , Marsal, K. & Kristoffersen, K (1984) Methodology and problems related to blood flow studies in the human fetus. *Ultrasound Med Biol* **10**, 329-338

Fitzgerald, D. E., Stuart, B , Drumm, J E. & Diugnan, N. M (1984) The assessment of the fetoplacental circulation with continuous wave Doppler ultrasound. *Ultrasound Med Biol* **10**, 371-386.

Giles, W. B , Trudinger, B J & Baird, P. J. (1985) Fetal umbilical artery flow velocity waveforms and placental resistance· pathological correlation. *Br J Obstet Gynaecol* **92**, 31-38

Gill, R. W., Trudinger, B J. & Garrett, W J. (1981) Fetal umbilical venous blood flow measured in utero by pulsed Doppler and B mode ultrasound. *Am J Obstet Gynecol* **139**, 720-725.

Gosling, R G. & King, D. H. (1975) Ultrasound angiology. In *Arteries and Veins* (Marcus, A. W. & Adamson, L., eds), Churchill Livingstone, Edinburgh, pp 61-98.

Griffin, D., Cohen-Overbeek, T. & Campbell, S. (1983) Uteroplacental bloodflow. *Clin Obstet Gynaecol* **10**, 565-602.

Griffin, D., Bilardo, K., Masini, L., Diaz-Recasens, J., Pearce, J. M. & Campbell, S (1984) Doppler bloodflow waveforms in the descending thoracic aorta of the human fetus. *Br J Obstet Gynaecol* **91**, 997-1006.

Hytten, F. E. & Leitch, I. (1971) *The Physiology of Human Pregnancy*, 2nd edn, Blackwell Scientific Publications, Oxford.

Marsal, K , Lindblad, A., Lingman, G. & Eik-Nes, S. H (1984) Bloodflow in the descending aorta; intrinsic factors affecting fetal bloodflow, i e. fetal breathing movements and cardiac arrythmia. *Ultrasound Med Biol* **10**, 339-348

Mosteller, F & Tukey, J W (1977) *Data Analysis and Regression*, Addison-Wesley Co., Reading, Massachusetts, p. 209.

Olsen, R. M & Cooke, J. P. (1975) Human carotid artery diameter and flow by a non-invasive technique. *Med Instrum* **9**, 99-102

Pourcelot, L. (1974) Application cliniques de l'examen Doppler transcutané In *Vélocimétrie Ultrasonoré Doppler* (Perroneau, P., ed.), Séminaire INSERM, Paris, pp. 213-240.

Reuwer, P. J H. M., Bruinse, H W , Stoutenbeek, P & Haspels, A. A. (1984) Doppler assessment of the fetoplacental circulation in normal and growth-retarded fetus *Eur J Obstet Gynecol Reprod Biol* **18**, 199-205.

Royston, J. P (1983) A simple method of evaluating the Shapiro-Francia W' test of non-normality. *Statistician* **32**, 297-300.

Stuart, B., Drumm, J , Fitzgerald, D. E. & Duignan, N. M (1980) Fetal blood velocity waveforms in normal pregnancy. *Br J Obstet Gynaecol* **87**, 780-785.

Trudinger, B. J., Giles, W. B & Cook, C. M. (1985) Uteroplacental bloodflow velocity-time waveforms in normal and complicated pregnancy *Br J Obstet Gynaecol* **92**, 39-45.

Warsof, S. L., Pearce, J. M. F & Campbell, S. (1983) The present place of routine ultrasound screening. *Clin Obstet Gynaecol* **10**, 445-458.

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Normal range of fetal transcutaneous carbon dioxide tension during labour

CARSTEN NICKELSEN, TOM WEBER

Summary. Fetal transcutaneous carbon dioxide tension (tc-$P\text{co}_2$) was monitored during 122 deliveries, using an electrode temperature of 44°C in 80 cases and of 41°C in 42 cases. Significant correlations between tc-$P\text{co}_2$ and umbilical artery blood $P\text{co}_2$ were found using both electrode temperatures, but the regression lines indicated a larger and more inconstant CO_2-contribution from skin metabolism when the low electrode temperature was used. Normal range of tc-$P\text{co}_2$ was calculated at 41°C and 44°C electrode temperatures. Mean values of fetal tc-$P\text{co}_2$ were found to increase during normal labour, and especially in fetuses developing acidosis, but only four of six infants born with acidaemia had tc-$P\text{co}_2$ values exceeding the normal range.

Since the early 1960s fetal acid-base measurements have been used to assess fetal well-being (Saling 1961) Routine measurements of fetal capillary blood pH provide discontinuous pH values and involve incision in the fetal skin. Continuous tissue-pH monitoring has been used by some investigators (Weber *et al.* 1978; Nickelsen *et al.* 1985), but this method is also invasive. In contrast, continuous transcutaneous carbon dioxide monitoring is non-invasive, and close correlations have been demonstrated between fetal values measured during labour and fetal capillary and umbilical artery blood values (Nickelsen *et al* 1986). During fetal respiratory (hypercapnic) acidosis the transcutaneous carbon dioxide tension (tc-$P\text{co}_2$) is elevated by definition, but also—at least temporarily—during fetal metabolic acidosis an elevation of tc-$P\text{co}_2$ will be found (Saling 1966; Nickelsen & Weber 1987*a*). In this paper we report the normal range of fetal tc-$P\text{co}_2$ during uncomplicated deliveries and the changes of tc-$P\text{co}_2$ during labour associated with the birth of acidaemic infants.

Subjects and methods

Following informed consent 122 women in labour at between 36 and 42 weeks gestation participated in the study. There was no selection procedure, consecutive patients who were willing to participate were recruited when the investigator was able to be present in the labour ward during the whole of labour and delivery In this way both high- and low-risk patients were included. Of the 122 women 76 were primigravid, 26 were para 1 and 20 were para 2 to 4 The mean age was 27 years, the mean duration of the first stage was 503 min (range 90–1040) and the mean duration of the second stage was 29 min (2–120). Eleven women were delivered by caesarean section (two because of suspected fetal hypoxia and nine because of dystocia) and 29 were delivered by vacuum extraction (13 because of suspected fetal hypoxia and 16 because of a prolonged second stage of labour).

Before monitoring, the electrode (Radiometer E5230) was calibrated by either two-step calibration (5% and 10% CO_2 gas mixture) ($n = 80$) or by one-step calibration (5% CO_2 gas mixture followed by an electrode sensitivity test by

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Department of Obstetrics and Gynaecology, Rigshospitalet, University of Copenhagen, Denmark
CARSTEN NICKELSEN
TOM WEBER

Correspondence Carsten Nickelsen, Department of Obstetrics and Gynaecology, Rigshospitalet, 9 Blegdamsvej, DK-2100 Copenhagen Ø, Denmark

exposing the electrode to the 10% CO_2 gas mixture) ($n = 42$). The electrode was sterilized by fluid aldehydes (Korsolin 3% during 20 min) and the electrode membrane was renewed between monitorings. When the cervical dilatation was ≥4 cm and the membranes were ruptured, the electrode was attached to the fetal head by a suction ring (Nickelsen & Weber 1987*b*). The monitor (Radiometer TCM 220) was connected to the cardiotocograph (Hewlett Packard 8030A) and the tc-$P\mathrm{co}_2$ plotted in the cardiotocogram (Nickelsen *et al.* 1985). The fetal heart rate was monitored using direct fetal ECG by a spiral electrode.

The electrode temperature was 44°C during the first 80 monitorings and 41°C during the last 42. During labour the cervical dilatation was estimated by frequent vaginal examinations and noted in the cardiotocogram. Active pushing was not permitted before full dilatation (10 cm) was verified by vaginal examination. In some women each cm of cervical dilatation from electrode application until full dilatation was not verified by vaginal examination, but as the tc-$P\mathrm{co}_2$ tracing was usually stable between examinations in these women, the tc-$P\mathrm{co}_2$ value corresponding to each cm of dilatation was known. The electrode stabilization time (Nickelsen *et al.* 1986) and the electrode drift were calculated after each monitoring.

Immediately after birth the umbilical cord was clamped and blood samples were collected from the umbilical artery and vein and analysed in a blood gas analyser (Radiometer ABL3). The mean values of tc-$P\mathrm{co}_2$ for each cm of cervical dilatation were calculated separately for fetuses monitored at 44°C and 41°C electrode temperature. All tc-$P\mathrm{co}_2$ values were corrected to a temperature of 37°C using the anaerobic temperature coefficient of CO_2 in blood (Siggaard-Andersen 1974; Nickelsen *et al.* 1986). Correlation with umbilical artery $P\mathrm{co}_2$ was calculated for patients in whom the tc-$P\mathrm{co}_2$ was monitored until just before delivery.

The normal range of fetal tc-$P\mathrm{co}_2$ was defined as the mean ± 2 SD calculated from all births with an umbilical artery blood pH >7·19. The influence of epidural analgesia and meconium-stained amniotic fluid was assessed by calculating mean values especially for these groups of patients which included deliveries with low umbilical artery blood pH values.

Statistics

The distribution of the tc-$P\mathrm{co}_2$ values was obtained at each cm of cervical dilatation by plotting the values on to probability paper for normal (Gaussian) distribution. Changes in tc-$P\mathrm{co}_2$ values were evaluated during the first and second stage of labour by a paired *t*-test between the first measured value and the value

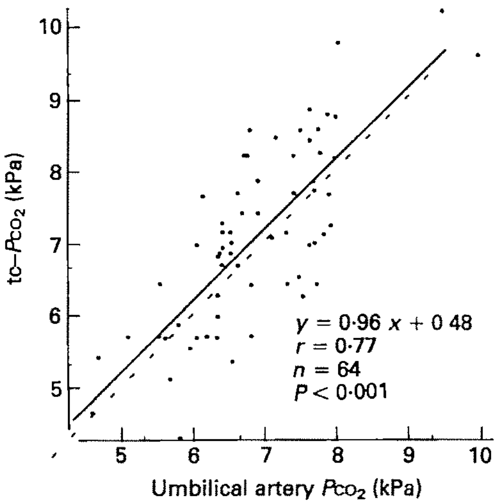

Fig. 1. Correlation between umbilical artery blood $P\mathrm{co}_2$ and transcutaneous carbon dioxide tension (tc-$P\mathrm{co}_2$) at delivery. The tc-$P\mathrm{co}_2$ was measured at 44°C and corrected to 37°C.

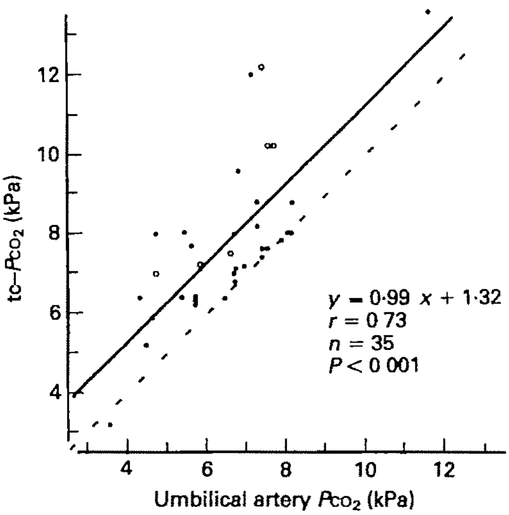

Fig. 2. Correlation between umbilical artery blood $P\mathrm{co}_2$ and tc-$P\mathrm{co}_2$ at delivery. The tc-$P\mathrm{co}_2$ was measured at 41°C and corrected to 37°C. ○, Electrode drift >0·4 kPa; ●, electrode drift <0·05 kPa.

at full dilatation (verified by vaginal examination) (first stage changes) and between the value at full dilatation and the last measured value just before delivery (second stage changes) (significance level $P<0{\cdot}05$). Differences in mean values obtained in relation to epidural analgesia and meconium staining were evaluated by a two-sample t-test (significance level $P<0{\cdot}05$).

Results

Technical problems with the electrode and too short monitoring periods caused exclusion of seven patients. A slight fetal acidosis (umbilical artery blood pH between 7·15 and 7·19 inclusive) was found in 12 infants, and more manifest acidosis (pH <7·15) was diagnosed in six infants. Normal range of fetal tc-$P\text{CO}_2$ was calculated for the remaining 97 fetuses. In 33 women the electrode was applied at a cervical dilatation of 4 cm, and only seven women had a cervical dilatation of >8 cm at the start of monitoring. The electrode was removed before full dilatation in the 11 women who were delivered by caesarean section and in 17 women monitoring was discontinued before the end of the second stage as the electrode fell off and was not re-applied. The values obtained for each cm of cervical dilatation had a near normal distribution. The normal ranges, defined as the mean ± 2 SD calculated from fetuses born with umbilical artery blood

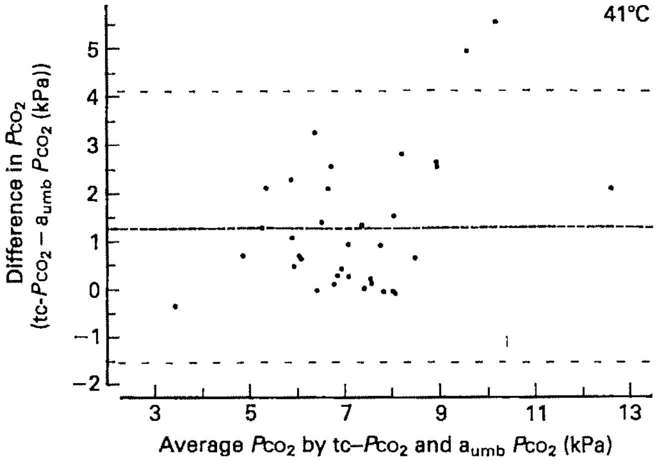

Fig. 3. The difference between tc-$P\text{CO}_2$ and umbilical artery blood $P\text{CO}_2$ against the average between tc-$P\text{CO}_2$ and umbilical artery blood $P\text{CO}_2$ when using 41°C electrode temperature (all values in kPa corrected to 37°C). The mean ± 2 SD is marked as broken lines

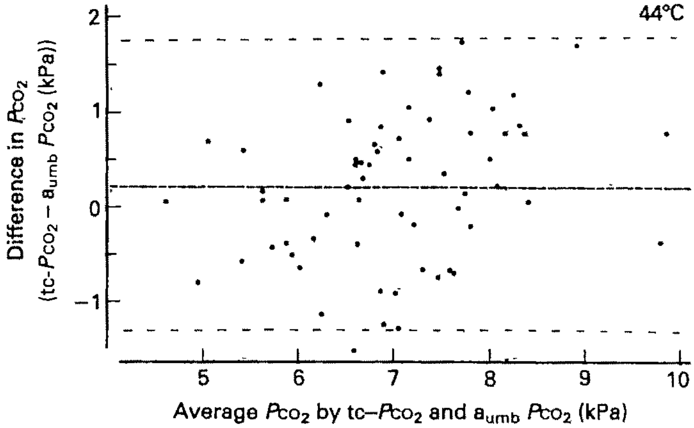

Fig. 4. The difference against the mean (see Fig. 3) when using 44°C electrode temperature.

pH >7·19, are presented in Table 1. The normal range is wide, especially with the low electrode temperature (all values are corrected to 37°C). There was a statistically significant change in tc-$P\text{CO}_2$ during the first stage of labour at both electrode temperatures (41°C: t = 2·14, DF = 32; 44°C: t = 3·52, DF = 57, two-tailed paired t-test). The mean increase of tc-$P\text{CO}_2$ per cm of cervical dilatation was 0·16 kPa at 41°C, and 0·11 kPa at 44°C. The change in tc-$P\text{CO}_2$ during the second stage of labour was also significant in both series (41°C: t = 2·11, DF = 29; 44°C: t = 2·03, DF = 38). The mean increase during the second stage was 0·45 kPa and 0·71 kPa respectively.

The correlations between tc-$P\text{CO}_2$ measured just before delivery or caesarean section and umbilical artery blood $P\text{CO}_2$ are illustrated in Figs 1 and 2. Infants born with a low pH are included, but in 16 women monitoring was discontinued more than 10 min before delivery, and these values are not included. Significant correlations were found at both electrode temperatures, and the regression lines were both parallel to the identity line, but the intercept on the y-axis was higher, when the low temperature was used. A plot of the difference between the transcutaneous value and the blood value against their mean value (Figs 3 & 4) shows more about the agreement between the two methods (Bland & Altman 1986). The mean (SD) of the difference was 1·28 (1·40) kPa when using the low electrode temperature and 0·21 (0·78) kPa when using the high electrode temperature.

Four infants monitored at 44°C were born with an umbilical artery blood pH <7·15. In all four of these the tc-$P\text{CO}_2$ increased during labour (Fig. 5) but the normal range was exceeded only in two of them. Two fetuses monitored with an electrode temperature of 41°C had an umbilical artery blood pH <7·15, and despite the wide limits of normal range, the tc-$P\text{CO}_2$ exceeded the limits in both (Fig. 6). The mean duration of labour for these six acidotic infants was 642 min (range 380–900) for the first stage and 50 min (20–100) for the second stage.

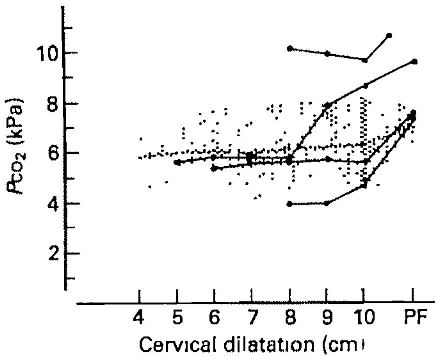

Fig. 5. Changes in fetal tc-$P\text{CO}^2$ during labour in four infants born with umbilical artery pH <7·15 The dotted area represents normal range of tc-$P\text{CO}_2$ Electrode temperature 44°C. PF, End of second stage.

Only two of the 12 newborn infants born with slight acidosis (umbilical artery blood pH between 7·15 and 7·19 inclusive) had tc-$P\text{CO}_2$ values exceeding the normal range, and both were monitored with an electrode temperature of 44°C.

During labour meconium staining of the amniotic fluid was observed in 18 women, but significantly higher values of tc-$P\text{CO}_2$ were only found at 8 cm of cervical dilatation monitored at 44°C and at full dilatation at 41°C (Table 2). Only two of these infants had a low umbilical artery pH (in one of them the tc-$P\text{CO}_2$ exceeded normal values).

The mean value of fetal tc-$P\text{CO}_2$ seems higher during deliveries associated with epidural analgesia than in those without analgesia (except N_2O and pudendal block). The mean values are presented in Table 2 and the difference was significant in 4 of 15 comparisons. The mean electrode drift was −0·14 (SD 0·56) kPa at 44°C and 0·10 (SD 0·32) kPa at 41°C. The duration of the monitoring did not affect the drift. The median 95% stabilization time was 2·1 min (interquartile range 1·5–2·5) at 44°C and 2·6 min (interquartile range 1·9–4·6) at 41°C.

Discussion

Previously fetal capillary carbon dioxide tension has been measured by fetal blood sampling. These values were not continuously measured, and all studies have been limited to small numbers of deliveries. According to the theory of transcutaneous measurements (Nickelsen *et al.* 1986) capillary blood values of $P\text{CO}_2$ are lower than transcutaneous values because of the carbon dioxide production in the skin. A significant increase of $P\text{CO}_2$ during labour could not be demonstrated in studies measuring capillary blood $P\text{CO}_2$ (Fig. 7), but one previous study of tc-$P\text{CO}_2$ monitoring demonstrated values at the same level as found in our study (Schmidt 1987).

Higher mean values were found when using

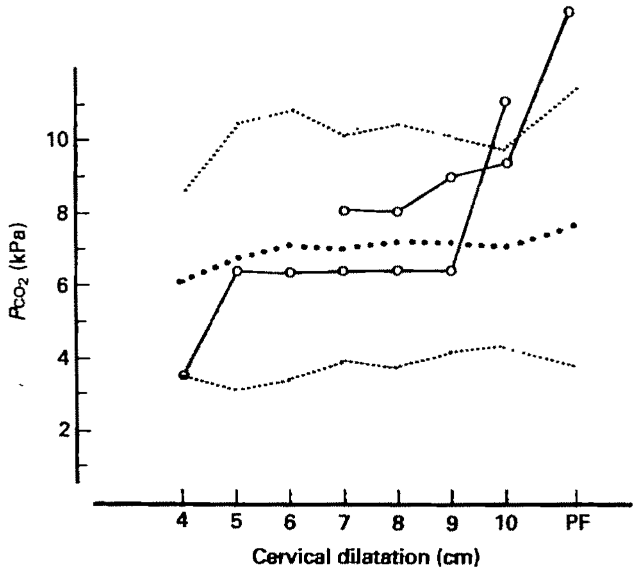

Fig. 6. Changes in fetal tc-Pco$_2$ during labour in two infants born with umbilical artery blood pH <7·15. The broken lines represent the limits of normal range. Electrode temperature 41°C. PF, End of second stage.

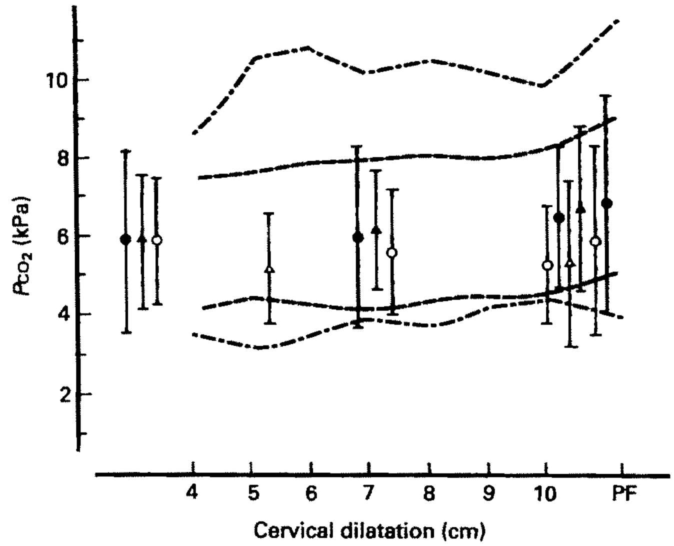

Fig. 7. Mean value of fetal capillary blood Pco$_2$, in relation to cervical dilatation The broken lines represent the normal range of tc-Pco$_2$. — · — ·, 41°C; — — — —, 44°C; ●, Saling 1964; ▲, Kubli 1966; ○, Beard & Morris 1965; △, Gårdmark 1974; PF, End of second stage of labour.

the low electrode temperature. To some degree this difference may be caused by patient variation because the SD of umbilical artery Pco$_2$ was larger in the study where the low electrode temperature was used. The position of the regression lines in Figs 1 and 2 demonstrated differences in intercepts on the *y*-axis indicating a larger constant difference between transcutaneous and arterial values when the low electrode temperature is used. The higher mean value and larger SD of the difference between the transcutaneous and the blood value of CO$_2$ when using 41°C electrode temperature (Fig. 3) indicates a less accurate monitoring at the low

Table 1. Mean (SD) and normal range of fetal tc-Pco_2 and umbilical artery blood Pco_2 in fetuses born with umbilical artery blood pH>7·19 (kPa corrected to the 37°C value)

Electrode temperature		tc-Pco_2 (kPa) at cervical dilatation (cm) 4	5	6	7	8	9	10	Delivery	Umbilical artery Pco_2 (kPa)
41°C	Mean (SD)	6·09 (1·25)	6·80 (1·82)	7·10 (1·85)	6·98 (1·53)	7·13 (1·67)	7·19 (1·46)	7·10 (1·34)	7·61 (1·89)	6·18 (1·19)
	n	17	23	26	28	30	31	32	30	36
	Normal range	3·59–8·59	3·16–10·44	3·40–10·8	3·92–10·04	3·79–10·47	4·27–10·11	4·42–9·78	3·83–11·39	3·80–8·56
44°C	Mean (SD)	5·80 (0·84)	5·99 (0·78)	6·01 (0·93)	5·98 (0·94)	6·16 (0·94)	6·19 (0·88)	6·30 (0·93)	6·99 (0·99)	6·64 (0·98)
	n	16	30	41	45	52	56	54	39	61
	Normal range	4·12–7·48	4·43–7·55	4·15–7·87	4·10–7·86	4·28–8·04	4·43–7·95	4·44–8·16	5·01–8·97	4·48–8·40

Table 2. Mean (SD) of fetal tc-Pco_2 during labour according to staining of the amniotic fluid and maternal epidural analgesia

Electrode temperature	Variable	tc-Pco_2 (kPa) at cervical dilatation (cm) 4	5	6	7	8	9	10	Delivery
41°C	Stained fluid								
	Absent	6·22 (1·17)	6·91 (1·66)	7·18 (1·71)	7·09 (1·42)	7·03 (1·35)	7·11 (1·33)	7·18 (1·45)	7·71 (2·03)
	n	20	27	29	31	31	32	33	30
	Present	4·90	4·90	5·50 (0·99)	6·20 (1·40)	8·05 (2·90)	8·18 (1·77)	8·55 (1·17)	9·05 (2·26)
	n	1	1	2	3	4	4	4	4
	t				1·038	1·234	1·468	1·812*	1·226
44°C	Stained fluid								
	Absent	5·80 (0·78)	5·99 (0·76)	6·08 (0·91)	6·06 (0·93)	6·31 (1·14)	6·24 (1·06)	6·38 (1·04)	7·10 (1·12)
	n	16	29	38	41	51	56	55	37
	Present	5·99 (1·21)	5·87 (0·70)	5·74 (0·73)	5·58 (0·64)	5·62 (0·83)	6·01 (1·00)	6·34 (1·20)	7·41 (1·16)
	n	2	5	9	11	12	12	11	11
	t		0·329	1·041	1·607	1·972*	0·688	0·114	0·800
41°C	Epidural								
	Absent	5·98 (1·20)	6·46 (1·54)	6·80 (1·60)	6·84 (1·27)	6·84 (1·15)	7·10 (1·24)	7·13 (1·22)	7·76 (2·03)
	n	12	18	23	26	27	28	28	27
	Present	6·40 (1·16)	7·52 (1·77)	7·84 (1·91)	7·59 (1·81)	8·18 (2·34)	7·66 (1·89)	7·96 (2·04)	8·29 (2·29)
	n	9	10	8	8	8	8	9	7
	t	0·805	1·656	1·508	1·319	2·243*	0·999	1·495	0·600
44°C	Epidural								
	Absent	5·76 (0·80)	5·92 (0·73)	5·98 (0·90)	5·91 (0·87)	6·12 (1·14)	6·10 (1·07)	6·26 (1·03)	7·12 (1·13)
	n	16	30	43	48	57	58	56	39
	Present	6·34 (0·71)	6·38 (0·87)	6·98 (0·68)	6·52 (1·14)	6·68 (0·76)	6·74 (0·76)	7·00 (1·00)	7·40 (1·15)
	n	2	4	4	4	6	10	10	9
	t		1·161	2·157*	1·319	1·172	1·809*	2·101*	0·668

Significance of difference $^*P<0·05$, two-sample *t*-test.

temperature. The temperature factor used for correction of the elevated electrode temperature is based on the anaerobic temperature coefficient of carbon dioxide in blood, and does not take into account any changes in the metabolic production of carbon dioxide in the upper layer of epidermis. Our results seem to indicate a larger and more inconstant production of CO_2 in the skin at 41°C than at 44°C, but this could more likely be a consequence of an inconstant lower blood flow (decreased removal of the CO_2 produced in the skin by capillary blood). Schmidt (1987) also found that a lower electrode temperature was associated with a higher tc-$P\mathrm{co}_2$ value (after correction for temperature). However, the difference in agreement with blood values indicates that normal range must be defined separately for each electrode temperature.

Using 44°C electrode temperature at neonatal monitoring, skin burns from the electrode have been observed, and monitoring at lower temperatures is preferable. In fetal transcutaneous monitoring skin burns have been reported only in one case (S. Schmidt, personal communication) and because of the better agreement with blood values the 44°C electrode temperature might be preferable. Saling (1966) noted that fetal carbon dioxide tension increased, at least temporarily, during the development of fetal acidosis. In our study, four of the six infants born with an acidotic umbilical artery pH had tc-$P\mathrm{co}_2$ values exceeding the normal values, and the other two had distinctly increasing values, but because they had low tc-$P\mathrm{co}_2$ levels during the first stage of labour the final values remained within the normal range. A distinct increase of tc-$P\mathrm{co}_2$ might be a better index for fetal acidosis than the actual value of tc-$P\mathrm{co}_2$. Only one of the six infants had a severe acidosis (pH = 7·01) and the final tc-$P\mathrm{co}_2$ in this fetus was 13·6 kPa.

In line with the different normal values found at the different electrode temperatures, different cut-off levels for a 'pathological' tc-$P\mathrm{co}_2$ are indicated. Because of the very few acidotic infants it is not possible to calculate the sensitivity and specificity of the test.

Different cut-off 'pathological' $P\mathrm{co}_2$ levels according to the cervical dilatation are impractical for routine use, and the mean +SD when the tc-$P\mathrm{co}_2$ is highest (end of second stage) might be suggested as a limit for 'pathological' tc-$P\mathrm{co}_2$. In our institution the limit would be 8 kPa with the 44°C electrode temperature and 9·5 kPa when electrode temperature is 41°C (both values are corrected to 37°C values).

Using these limits four of the six acidotic infants would have been detected, but several other infants (16%) without acidosis also exceeded the limit. In a previous larger study of umbilical artery blood $P\mathrm{co}_2$ (Nickelsen & Weber 1987*a*) the suggested limit of pathological tc-$P\mathrm{co}_2$ was 7·7 kPa.

In a study using fetal capillary blood analysis (Gårdmark 1974) elevated mean values of capillary blood $P\mathrm{co}_2$ were found in association with meconium-stained amniotic fluid; this was not found in our study, and the mean pH of umbilical artery blood measured in these infants was not different from that of other infants.

We found elevated fetal tc-$P\mathrm{co}_2$ values during epidural analgesia. These changes corroborate the theory that epidural analgesia, eliminating the pain during delivery, changes the maternal respiration. Consequently, the decreased maternal $P\mathrm{co}_2$ induced by hyperventilation will be less pronounced, and fetal $P\mathrm{co}_2$ will increase (Thomsen & Weber 1984).

We conclude that fetal tc-$P\mathrm{co}_2$ increases during both first and second stage of labour. Usually a fetal acidosis is reflected as increasing tc-$P\mathrm{co}_2$ values, but because of the relatively wide range of normal tc-$P\mathrm{co}_2$, the limits for pathological tc-$P\mathrm{co}_2$ will only be exceeded in some cases (presumably always in severe acidosis). Fetal acidosis is most safely monitored, when both the tissue-pH and the tc-$P\mathrm{co}_2$ are monitored (Nickelsen *et al.* 1985).

References

Beard, R. W. & Morris, D E. (1965) Foetal and maternal acid-base balance during normal labour. *J Obstet Gynaecol Br Commonw* **72**, 496-506

Bland, J. M. & Altman, D G. (1986) Statistical methods for assessing agreement between two methods of clinical measurement *Lancet* **i**, 307-310

Gårdmark, S. (1974) Fetal and maternal acid-base balance, carbohydrate and lipid metabolism in relation to different signs of fetal distress during labour. In *Studies on Acid-Base Balance, Carbohydrate and Lipid Metabolism in Human Fetal and Maternal Blood in Clinical and Experimental Conditions During Labour.* Studentlitteratur, Malmø, pp 145-183.

Kubli, F. (1966) Intrapartale Asphyxia und ihre Diagnose. In *Fetale Gefahrenzustande und ihre Diagnose* Georg Thieme, Stuttgart, pp. 49-88.

Nickelsen, C., Thomsen, S. G. & Weber, T. (1985) Continuous acid-base assessment of the human fetus during labour by tissue pH and transcutaneous carbon dioxide monitoring. *Br J Obstet Gynaecol* **92,** 220-225.

Nickelsen, C., Thomsen, S. G. & Weber, T. (1986) Fetal carbon dioxide tension during human labour. *Eur J Obstet Gynecol Reprod Biol* **22,** 205-216.

Nickelsen, C. & Weber, T (1987*a*) Acid-base evaluation of umbilical cord blood. Relation to delivery mode and Apgar scores. *Eur J Obstet Gynecol Reprod Biol* **24,** 153-165.

Nickelsen, C. & Weber, T. (1987*b*) Suction fixation of the tc-$P\text{co}_2$ electrode for fetal monitoring *J Perinat Med* **15,** 383-389.

Saling, E. (1961) Neue Untersuchungsmoglichkeiten des Kindes unter der Geburt (Einführung und Grundlagen). *Geburtshilfe Frauenheilkd* **21,** 905.

Saling, E. (1964) Die Blutgasverhaltnisse und der Saure-Basen-Haushalt des Feten bei ungestörtem Geburtsablauf. *Geburtsh Gynaecol* **161,** 262-292.

Saling, E. (1966) *Das Kind im bereich der Geburtshilfe.* Georg Thieme Verlag, Stuttgart.

Schmidt, S. (1987) Clinical experience on tc-$P\text{co}_2$ during labour. *J Perinat Med* **15,** 395-401.

Siggaard-Andersen, O. (1974) *The Acid Base Status of the Blood.* 4th edn. Munksgård, Copenhagen.

Thomsen, S G. & Weber, T (1984) Fetal transcutaneous carbon dioxide tension during the second stage of labour *Br J Obstet Gynaecol* **91,** 1103-1106.

Weber, T., Hahn-Pedersen, S. & Bock, J. E (1978) Continuous fetal tissue pH recording during labour. *Br J Obstet Gynaecol* **85,** 770-772

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Plasma fructosamine in non-diabetic pregnancy

M. J. STALEY, F. MURRAY-ARTHUR

Summary. Plasma fructosamine and its relation to plasma total protein and albumin was examined in 40 non-diabetic pregnant women. Plasma fructosamine did not correlate with haemoglobin A_1 or plasma albumin. The mean intra-individual ranges were plasma fructosamine 0·53 mmol/l (SD 0·17); haemoglobin A_1 1·42% (SD 0·42); plasma fructosamine/g albumin 0·024 mmol (SD 0·005) and plasma fructosamine/g total protein 0·008 mmol (SD 0·003). A high degree of individuality for these variables was also observed.

Plasma fructosamine has been reported to detect 85% of gestational diabetics (Roberts *et al.* 1983) compared with the oral glucose tolerance test which detects only 62% of cases (O'Sullivan *et al.* 1973). Plasma fructosamine measurement has the advantage of indicating blood glucose control over the previous 2–3 weeks, which is clinically advantageous during pregnancy. Fructosamine ranges for good carbohydrate control in pregnant women have been reported as being constant during the first 8 weeks gestation with a slight fall during the second and third trimester (Roberts & Baker 1986).

Plasma fructosamine is a measure of glycated plasma proteins (Lim & Staley 1985) predominantly albumin (Johnson *et al.* 1986). It is well known that plasma protein and albumin concentrations fall by up to 30% during pregnancy although concentrations of other proteins increase. Several groups have found a correlation between plasma fructosamine and albumin in non-pregnant diabetics and as a consequence, correction factors have been applied to allow for the effect of albumin concentration (van Dieijen-Visser *et al.* 1986*a*; Howey *et al.* 1987). Other workers have shown that plasma fructosamine does not correlate with albumin concentration in non-diabetic subjects (Winocour *et al.* 1987) and it has been proposed that plasma fructosamine and albumin correlate only when the half-life of circulating plasma albumin is reduced, as occurs with protein losing states such as the proteinuria of nephrotic syndrome (Johnson *et al.* 1986).

If plasma fructosamine measurement is to be used to indicate blood glucose control during pregnancy, the effect of decreasing plasma albumin and total protein concentration on the estimation of plasma fructosamine during pregnancy needs to be determined.

The intra-individual variation of plasma fructosamine in non-pregnant, non-diabetic subjects is known to be large, which has led to the suggestion that a reference range for plasma fructosamine in pregnancy will not enable small increases in blood glucose to be detected (Howey *et al.* 1987). This study reports the intra-individual variation of plasma fructosamine and its relation to plasma albumin, total protein and haemoglobin A_1 (HbA_1) in a study of 40 pregnant, non-diabetic subjects.

Subjects and methods

Women without any previous history of diabetes mellitus or gestational diabetes presenting to the antenatal clinic were invited to participate in the study. Informed consent was obtained for blood samples to be collected monthly during their pregnancy. A total of 57 women was enrolled in

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Department of Clinical Chemistry, Royal Hobart Hospital, Hobart, Tasmania 7000, Australia
M. J. STALEY *Scientific Officer*

Department of Obstetrics and Gynaecology, Faculty of Medicine, University of Tasmania, Hobart, Tasmania 7000, Australia
F. MURRAY-ARTHUR *Senior Lecturer*

Correspondence: M. J. Staley

the study, 17 withdrew due to miscarriage or other reasons, leaving 40 subjects (mean age 24, range 17–38 years). None of the remaining subjects showed glycosuria or any other clinical signs of carbohydrate intolerance during the course of the study and their infants were normal with a mean birthweight of 3340 g (range 2590–4200 g).

Blood samples were taken with a minimum of venous stasis whilst the subjects were sitting. The samples were anticoagulated with EDTA (fructosamine, HbA_1) or allowed to clot at room temperature (albumin, total protein). Serum and plasma samples were separated without delay and the samples were stored for <48 h at 4 °C before analysis which was performed in batches.

Plasma fructosamine was measured by a modification (Lim & Staley 1985) of the method described by Johnson *et al.* (1982), HbA_1 by mini column (Bio-Rad product No. 1917001), plasma albumin by rate nephelometry (Beckman Immunochemistry System, Fullerton, CA 22634, USA) and plasma total protein by continuous-flow analysis (Technicon Instruments Corp., Tarrytown, NY 10591, USA).

All methods were monitored for quality during the course of the study by including two levels of quality control material into each batch of analysis. Inter-run precision was: plasma fructosamine 1·46 mmol/l (SD 0·07), 2·89 mmol/l (SD 0·14), HbA_1 7·71% (SD 0·62), 13·17% (SD 1·01), immunospecific albumin 40·0 g/l (SD 2·09) and total protein 49 g/l (SD 1·7), 76 g/l (SD 2·7).

Plasma fructosamine/g albumin or plasma fructosamine/g total protein was determined by dividing plasma fructosamine (mmol/l) by plasma albumin or total protein (g/l).

Student's paired *t*-test was used for comparison of means, and correlations were determined by linear regression analysis with the least squares method. Probability <0·05 was accepted as statistically significant.

Results

During pregnancy, mean monthly plasma fructosamine concentrations did not change significantly. The mean HbA_1 of all pregnancies decreased from 6·6% at 8 weeks to 6·3% at 20 weeks ($P<0{\cdot}05$) and to 6·1% at 24 weeks ($P<0{\cdot}01$). Thereafter mean HbA_1 was not statistically significantly different from the value at 8 weeks (Fig. 1).

The mean plasma albumin of all pregnancies decreased from 39·1 g/l at 8 weeks to 35·4 g/l at 16 weeks ($P<0{\cdot}001$). It continued to decrease so that at term, the mean concentration was 8 g/l lower than at 8 weeks gestation (Fig. 2).

At 8 weeks gestation, the mean plasma fructosamine/g albumin of all pregnancies was 0·040 mmol/g which increased to 0·045 mmol/g at 16 weeks ($P<0{\cdot}01$) and 0·053 mmol/g at 36 weeks ($P<0{\cdot}001$) (Fig. 2).

The mean fructosamine/g total protein increased from 0·022 mmol/g at 8 weeks to 0·024 mmol/g protein at 28 weeks ($P<0{\cdot}01$) and 0·024 mmol/g protein at 36 weeks ($P<0{\cdot}01$) (Fig. 2).

Figure 3 shows the mean and range of values for plasma fructosamine, plasma fructosamine related to protein and albumin concentration and HbA_1, for each of the 40 non-diabetic pregnant women. The mean and maximum intra-

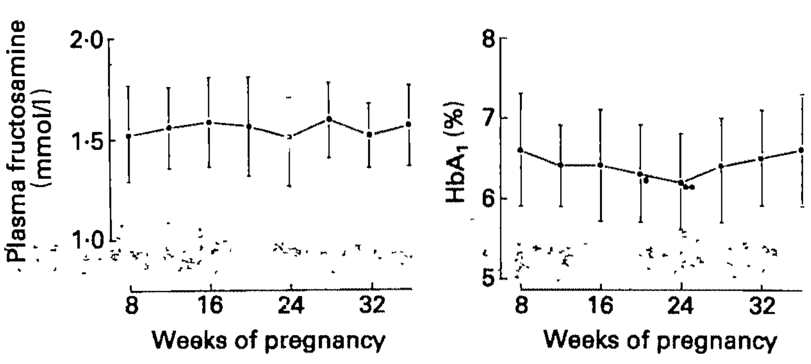

Fig. 1. Mean plasma fructosamine and HbA_1 in 40 non-diabetic pregnant women (mean, SD) between 8 and 36 weeks gestation. *t*-test comparison with value at 8 weeks: $^*P<0{\cdot}05$, $^{**}P<0{\cdot}01$.

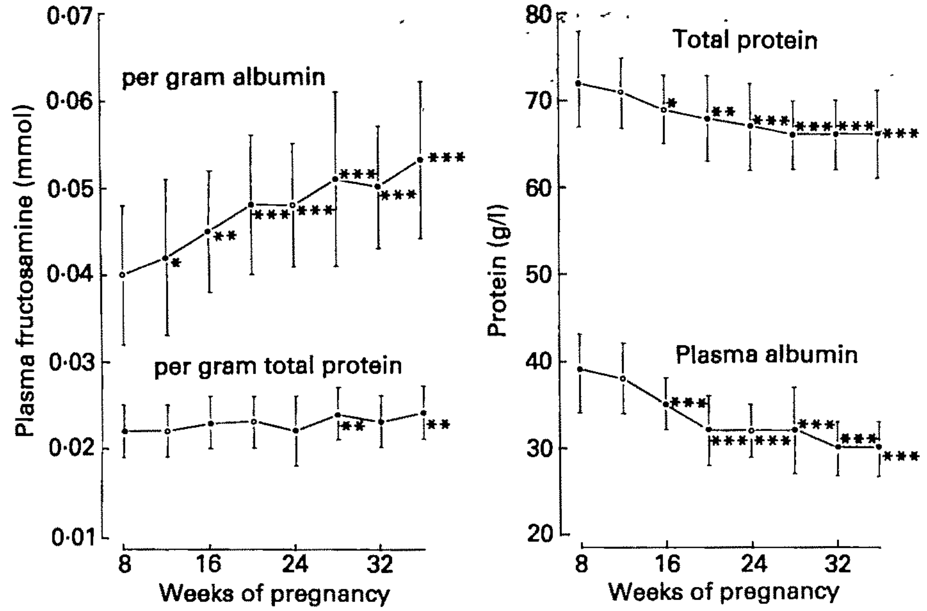

Fig. 2. Plasma albumin, total protein, fructosamine/g albumin and fructosamine/g total protein in 40 non-diabetic pregnant women (mean, SD). *t*-test comparison with value at 8 weeks: $^*P<0·05$, $^{**}P<0·01$, $^{***}P<0·001$.

individual range for plasma fructosamine, HbA_1, plasma fructosamine/g albumin and plasma fructosamine/g total protein were 0·53, 0·9 mmol/l; 1·4%, 2·2%; 0·024, 0·044 mmol; and 0·008, 0·016 mmol respectively (Table 1).

Plasma fructosamine did not correlate with plasma albumin ($r = 0·0613$, $P>0·1$) but plasma fructosamine correlated weakly with plasma total protein ($r = 0·1658$, $P<0·01$).

Discussion

Glycated plasma protein has been found to correlate significantly with plasma glucose in pregnant and non-pregnant diabetic subjects (Morris *et al.* 1985). Plasma fructosamine is a measure of glycated plasma proteins and its estimation during the antenatal period has been proposed as a means of discriminating women with gestational diabetes (Roberts *et al.* 1983; Roberts & Baker 1986; van Dieijen-Visser *et al.* 1986*a*) but all studies used a cross-sectional sample of women during pregnancy. Another study of glycated plasma proteins during pregnancy using an alternative technique found that the estimation was insensitive to slight changes in carbohydrate metabolism (Bourgeois *et al.* 1986).

We were unable to identify a significant change in the mean values of plasma fructosamine at defined weeks gestation which has been found by others using cross-sectional studies (Roberts & Baker 1986; van Dieijen-Visser *et al.* 1986*a*). Although mean, 4-weekly plasma fructosamine showed no significant variation (Fig. 1), individual patients had a range of plasma fructosamine which decreased by up to 0·9 mmol/l (−47%) during pregnancy whereas others showed an increase of up to 0·4 mmol/l (+26%) over the same period (Fig. 3). We were unable to find a common trend related to gestational age in our group of non-diabetic pregnant women.

For plasma fructosamine measurement to be of value for the detection of gestational diabetes, the intra- and inter-individual variation should be known. Recent work has shown that the inter-individual variation in non-diabetic, non-pregnant subjects gives a high index of individuality and as a consequence, population-based reference intervals are of little value and may be misleading (Howey *et al.* 1987). Our study shows that in non-diabetic pregnant subjects, this high degree of individuality is also present and makes the use of an overall reference range for plasma fructosamine during pregnancy difficult to apply.

Although plasma fructosamine is thought to be a measure of all glycated plasma proteins (Lim & Staley 1986), it is likely that only plasma

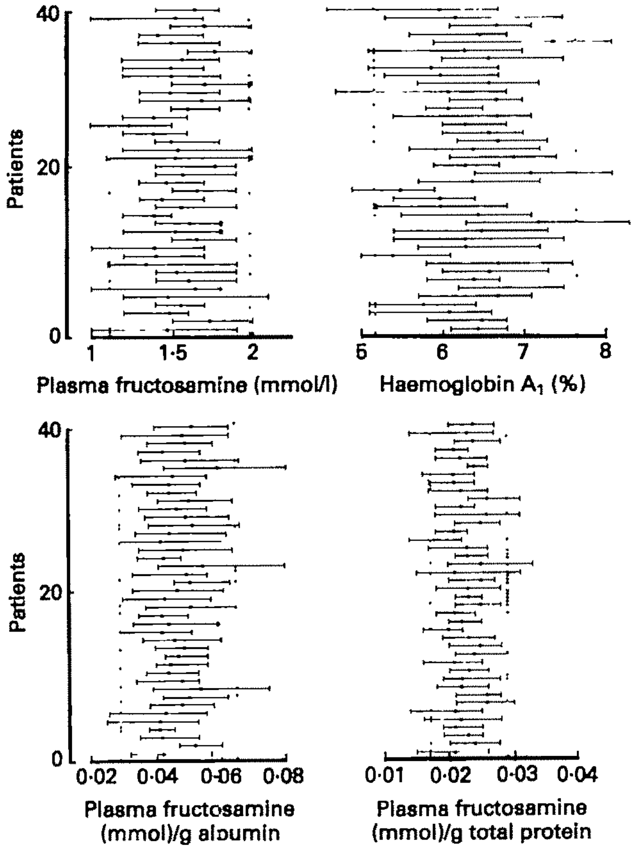

Fig. 3. Individual means and ranges for plasma fructosamine, HbA$_1$, plasma fructosamine/g albumin and plasma fructosamine/g total protein in 40 non-diabetic pregnant women between 8 and 36 weeks gestation

proteins with a prolonged half-life (albumin, IgG) will be significantly glycated.

As plasma albumin is thought to be the predominant plasma protein which is glycated and the major contributor to the fructosamine reaction (Johnson *et al.* 1986), several studies have investigated the interrelation of plasma albumin and fructosamine concentration, showing a significant correlation (van Dieijen-Visser *et al.* 1986*b*; Howey *et al.* 1987). These studies were on combined populations of diabetics and non-diabetics but in our study, where albumin concentrations varied from 22 to 49 g/l in a non-diabetic pregnant population, we were unable to show such a correlation ($r = 0·0613$, $P > 0·1$). Our results are to be expected as the glycation of

Table 1. Mean individual range during pregnancy of fructosamine, HbA$_1$, fructosamine/g albumin and fructosamine/g total protein in 40 pregnant women

	Range		
	Mean	Maximum	Minimum
Plasma fructosamine (mmol/l)	0·532	0·9	0·3
HbA$_1$ (%)	1·42	2·2	0·7
Fructosamine/g albumin (mmol)	0·024	0·044	0·005
Fructosamine/g total protein (mmol)	0·008	0·016	0·003

plasma protein is a first-order reaction, solely dependent upon the concentration of the open chain form of glucose which comprises approximately 0·001% of circulating plasma glucose (Angyal 1979). The molar concentration of plasma protein will always be in excess of open chain plasma glucose concentrations found in non-diabetic and diabetic subjects; hence the glycated plasma protein fraction will be independent of plasma protein concentration. Consequently, plasma fructosamine will be a reflection of plasma glucose concentration (open chain form) and the half-life of glycated plasma proteins. It has been shown that plasma fructosamine fluctuations may occur in non-diabetic patients where plasma glucose is normal and stable when in a hypercatabolic state (Lim & Staley 1985; Lloyd & Marples 1986) and in patients where plasma albumin half-life is known to be reduced such as nephrotic syndrome (Baker *et al.* 1983).

Our results show a significant reduction of plasma albumin concentration without a concomitant fall in plasma fructosamine. The mechanism for this is not clear, but may be due to altered protein synthesis and/or catabolism in pregnancy. An alternative explanation of the apparent increase of glycated albumin during pregnancy may be the production of plasma proteins with an increased affinity for glucose. The concentrations of other plasma proteins such as caeruloplasmin and other binding proteins may increase during pregnancy (Cox 1966) and their contribution to the fructosamine reaction has not been investigated in this study. Furthermore the plasma fructosamine reaction *in vitro* is most probably mediated by the formation of free radicals (Jones *et al.* 1987) and as caeruloplasmin is known to be a scavenger of free radicals, a reduced level of fructosamine may be expected as a consequence of in-vitro inhibition of the fructosamine reaction in those patients with an increased plasma caeruloplasmin.

On the basis of these results, any correction applied to plasma fructosamine for plasma albumin concentration (van Dieijen-Visser *et al.* 1986*b*; Howey *et al.* 1987) would be misleading.

Haemoglobin A_1 has been reported to both increase (Schwartz *et al.* 1976) and decrease (van Dieijen-Visser *et al.* 1986*a*, Worth *et al.* 1985) during normal pregnancy. The variable findings may be a consequence of small population size or cross-sectional rather than longitudinal studies. In our study, HbA_1 also shows a high degree of individuality in non-diabetic pregnant women which makes the use of an overall reference range during pregnancy difficult to apply.

Plasma fructosamine did not correlate with HbA_1 ($r = 0{\cdot}0559, P > 0{\cdot}1$) which is in contrast to a previous report (Lim & Staley 1985) that used mixed populations of diabetics and non-diabetics which appears to influence the relation of indices of glycation (Winocour *et al.* 1987).

The correction of fructosamine with plasma albumin or total protein does not improve the intra-individual variation for the derived measurements. Indeed, certain patients (23, 35) showed a greater intra-individual variation of fructosamine/g albumin than plasma fructosamine during the course of the pregnancy, indicating that in certain patients, the plasma fructosamine was constant whilst the plasma albumin decreased.

As a consequence of the high inter-individual variation for plasma fructosamine, HbA_1 and fructosamine related to plasma proteins, an overall reference range is difficult to apply during pregnancy.

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References

Angyal, S. J (1979) The composition of reducing sugars in solution In *Asymmetry in Carbohydrates* (Harmon, R. E., ed), Marcel Dekker, Inc , New York, pp 15-30

Baker, J R., O'Connor, J P , Metcalf, P A, *et al* (1983) Clinical usefulness of serum fructosamine concentration as a screening test for diabetes mellitus. *Br Med J* **287**, 863-867

Bourgeois, F J., Harbert, G M , Paulsen, E P *et al* (1986) Glycosylated serum protein level as a screening and diagnostic test for gestational diabetes mellitus *Am J Obstet Gynecol* **155**, 493-496

Cox, D W (1966) Factors influencing serum caeruloplasmin levels in normal individuals *J Clin Lab Med* **68**, 893-904

Howey, J E A , Browning, M C. K & Fraser, C. G (1987) Assay of serum fructosamine that minimises standardization and matrix problems: Use to assess components of biological variation. *Clin Chem* **33,** 269-272

Johnson, R N , Metcalf, P. A & Baker, J. R. (1982) Fructosamine. A new approach to the estimation of serum glycosylprotein. An index of diabetic control *Clin Chem Acta* **127,** 87-95

Johnson, R N., Metcalf, P. A & Baker, J R (1986) The contribution of albumin to serum fructosamine concentration. *Clin Biochem Rev* **7,** 90

Jones, A F., Winkles, J. W., Thornalley, P J. *et al.* (1987) Inhibitory effect of superoxide dismutase on fructosamine assay. *Clin Chem* **33,** 147-149

Lim, Y. S. & Staley, M. J. (1985) Measurement of plasma fructosamine evaluated for monitoring diabetes *Clin Chem* **31,** 731-733

Lim, Y. S. & Staley, M. J. (1986) Plasma fructosamine is a measure of all glycated proteins *Clin Chem* **32,** 560.

Lloyd, D. & Marples, J. (1986) Serum fructosamine and thyroid function. *Clin Chem* **32,** 1985.

Morris, M. A., Grandis, A. S. & Litton, J. (1985) The correlations of glycosylated serum protein and glycosylated hemoglobin concentrations with blood glucose in diabetic pregnancy *Am J Obstet Gynecol* **153,** 257-260.

O'Sullivan, J B., Mahan, C. M , Charles, D. *et al.* (1973) Screening criteria for high-risk gestational diabetic patients. *Am J Obstet Gynecol* **116,** 895-900.

Roberts, A B , Baker, J R , Court, D. J. *et al.* (1983) Fructosamine in diabetic pregnancy. *Lancet* **ii,** 998-1000

Roberts, A B & Baker, J R (1986) Serum fructosamine· A screening test for diabetes in pregnancy. *Am J Obstet Gynecol* **154,** 1027-1030

Schwartz, H. C., King, K. C , Schwartz, A. L *et al* (1976) Effects of pregnancy on haemoglobin A1C in normal, gestational diabetic, and diabetic women. *Diabetes* **25,** 1118-1122.

van Dieijen-Visser, M. P , Salemans, T , van Wersch, J W J *et al* (1986*a*) Glycosylated serum proteins and glycosylated haemoglobin in normal pregnancy. *Ann Clin Biochem* **23,** 661-666

van Dieijen-Visser, M. P , Seynaeve, C. & Brombacher, J (1986*b*) Influence of variations in albumin or total protein-concentration on serum fructosamine concentration (letter) *Clin Chem* **32,** 1610.

Winocour, P H., Bhatnagar, D , Reed, P *et al* (1987) Does the measurement of serum fructosamine accurately reflect levels of glycated albumin in insulin-dependent diabetes? *Ann Clin Biochem* **24,** 47-52.

Worth, R., Potter, J. M , Drury, J *et al* (1985) Glycosylated haemoglobin in normal pregnancy: A longitudinal study with two independent methods *Diabetologia* **28,** 76-79

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Early pregnancy termination: a comparison between vacuum aspiration and medical abortion using prostaglandin (16,16 dimethyl-trans-Δ_2-PGE$_1$ methyl ester) or the antiprogestogen RU 486

I. T. CAMERON, D. T. BAIRD

Summary. Three different regimens for termination of early pregnancy by medical means were compared to vacuum aspiration. Women seeking therapeutic abortion of pregnancy ($\leqslant$56 days amenorrhoea) were allocated to one of four treatment groups: (1) vacuum aspiration (n=28); (2) 1 mg vaginal pessary of a prostaglandin analogue (gemeprost) every 3 h for up to 5 pessaries (n=30); (3) the antigestogen (RU 486—mefipristone) 150 mg per day for 4 days by mouth (n=20); (4) RU 486 in the same dose as group 3 together with 1 mg gemeprost on day 3 (n=19). Complete abortion occurred more often in women treated with vacuum aspiration (96%), gemeprost alone (97%) and RU 486 plus gemeprost (95%) than in those treated with RU 486 alone (60%). In women receiving up to five gemeprost pessaries alone vomiting occurred in 7 (23%) and diarrhoea in 10 (33%); 16 (53%) required parenteral opiates for relief of pain. Side-effects and analgesic requirements were much reduced in the women who received RU 486 alone or in combination with a single gemeprost pessary. There was no difference in the number of days of vaginal bleeding after abortion between the four groups although there was wide individual variation (mean 10 days, range 1–34). These results confirm that medical induction of abortion in early pregnancy with prostaglandin vaginal pessaries is as effective as vacuum aspiration and that the dose can be reduced five-fold without loss of efficacy when used in combination with RU 486.

In the first trimester of pregnancy, therapeutic abortion is most often performed by vacuum aspiration of the uterus under general anaesthesia (OPCS 1985). Although the procedure is safe and highly effective (Paintin 1985), complications are related to both gestational age, and surgical and anaesthetic techniques (Grimes & Cates 1979). Consequently, and with the additional desire of many women to avoid operative treatment (Rosen *et al.* 1979), there has been much recent interest in the development of medical agents to interrupt the unwanted pregnancy at an early stage ('menstrual induction').

The prostaglandins (PGs) were the first agents to be used on a wide scale for medical abortion, but the inherent instability of the naturally occurring compounds and frequent gastrointestinal-associated side-effects limited their acceptability

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Department of Obstetrics and Gynaecology, University of Edinburgh, Centre for Reproductive Biology, 37 Chalmers Street, Edinburgh EH3 9EW, Scotland
I. T CAMERON *Lecturer*
D T. BAIRD *Professor*

Correspondence· Professor D T Baird

(Karim & Filshie 1970; Moscary & Csapo 1975). A variety of synthetic analogues has now been produced with improved stability and more specific uterine activity (Bygdeman *et al.* 1976, 1980; Csapo *et al.* 1982; Oshima *et al.* 1978). Although complete abortion can be induced in over 90% of women, widespread acceptance remains limited by troublesome side-effects (Bygdeman & Green 1979).

Antigestogens impair the action of progesterone on the pregnant uterus and hence offer an alternative approach to medical abortion (Csapo *et al.* 1973; Healy & Fraser 1985). Early clinical studies using the progesterone receptor antagonist RU 486 (17α-hydroxy-11β-(4-dimethylaminophenyl)-17α-(1-prop-1-ynyl) estra-4,9-dien-3-one, mifepristone) have confirmed the ability of this compound to induce myometrial activity and uterine bleeding, although the incidence of incomplete abortion (30%) is unacceptable (Kovacs *et al.* 1984). Improved results have been reported though in very early pregnancy (<40 days amenorrhoea) (Couzinet *et al.* 1986), and in studies using the drug in combination with a sub-therapeutic dose of intramuscular prostaglandin (Swahn *et al.* 1985).

The present study was designed to compare the efficacy and side-effects of vacuum aspiration under general anaesthesia for termination of early pregnancy (≤56 days amenorrhoea) with three different medical regimens, i.e. prostaglandin vaginal pessaries (16,16 dimethyl-trans-Δ_2-PGE$_1$ methyl ester, gemeprost) or RU 486 (mefipristone), both alone and in combination. Preliminary data for the RU 486-treated women have been described elsewhere (Cameron *et al.* 1986).

Patients and methods

The study included 100 women with pregnancies of less than 56 days amenorrhoea. Gestational age was assessed by menstrual history and clinical examination, with the addition of pelvic ultrasound if there was doubt clinically. Pregnancy was confirmed with an immunological pregnancy test (Hobson 1968). Patients with evidence of abnormal pregnancy or spontaneous abortion were excluded from study, as were women with medical complications such as cardiovascular or pulmonary disease, allergy or epilepsy. Pregnancy termination was indicated under the 1967 Abortion Act: local ethics committee approval was granted for the project, and written informed consent was obtained from each woman before treatment.

Once recruited, patients were allocated to the appropriate study group. The first 60 women were randomized to receive either 16,16 dimethyl-trans-Δ_2-PGE$_1$ methyl ester in pessary form, or vacuum aspiration under general anaesthesia. The next 40 women were treated with either RU 486 orally, or a combination of RU 486 with gemeprost. Although this group of patients was treated subsequent to the first 60, they were recruited from the same population source within 12 months of the original group using identical selection criteria.

Vacuum aspiration

Treatment was performed under general anaesthesia on an outpatient basis. The cervix was dilated to a maximum of 8 mm, and the uterine cavity was evacuated using a size 6 or 8 Karman cannula (Karman & Potts 1972). Pre-operative cervical priming was not used, but all women received either 10 units of oxytocin (Syntocinon; Sandoz Products Ltd) or 500 μg ergometrine maleate and 5 units of oxytocin (Syntometrine; Sandoz Products Ltd) immediately before, or during, the procedure itself.

Gemeprost pessaries

A single 1-mg pessary was placed in the posterior fornix of the vagina, and this treatment was repeated every 3 h until either the products of conception had been expelled, the frequency or severity of any side-effects became so great as to warrant cessation of therapy, or until a total of five pessaries had been given.

RU 486

The remaining 40 patients were randomly allocated to receive RU 486 alone, given orally at a dose of 150 mg daily for 4 days (n=20), or the same dose of RU 486 for 4 days, but in addition a single 1-mg gemeprost pessary administered 48 h after starting the antigestogen (n=20). The patients remained in hospital during the treatment period.

Prophylactic medication was not prescribed, but analgesics (paracetamol 1g; dihydrocodeine 30 mg; pethidine 100 mg or diamorphine 5 mg), anti-emetics (cyclizine 50 mg) or other preparations, such as anti-diarrhoeal agents, were administered as required. No dietary restriction was enforced.

After treatment all patients were given appropriate contraceptive advice, and arrangements were made for follow-up at 1 and 2 weeks, and then every 2 weeks thereafter, until the onset of the next menstrual period. Abortion was considered successful at the 2-week visit if there was minimal vaginal bleeding, the cervix was closed, the uterus normal in size, and the serum concentration (or urinary excretion) of hCG had fallen. In the event of treatment failure, the uterus was evacuated surgically under general anaesthesia.

Statistical analysis

Wilcoxon's rank sum test, the χ^2 test, and Fisher's exact probability test were used to analyse the results.

Results

Two women allocated to the vacuum aspiration group were excluded from the analysis because the pregnancy exceeded 56 days amenorrhoea by the time of surgery. Another woman allocated to the RU486 plus PG group was excluded from the analysis because her treatment was discontinued after 36 h due to side-effects before she received the PG pessary. The characteristics of the remaining subjects are shown in Table 1. There were no significant differences between the four study groups.

Vacuum aspiration

All 28 women received outpatient treatment as planned, without complication. Blood loss was not measured objectively, but in no case was transfusion or overnight observation required.

Prostaglandin pessary

Of the 30 women in this group 28 received the maximum five 1-mg pessaries. The other two women aborted gestational sacs after receiving the fourth pessary, and treatment was therefore discontinued.

Crampy period-like pain occurred after a median period of 240 (range 162–528) min, followed by vaginal bleeding after a median of 507 (range 267–1440) min. Only 4 (13%) women required no pain relief during treatment—14 (47%) were prescribed oral medication whereas 16 (53%) required parenteral opiates.

Vomiting occurred in 7 (23%) and diarrhoea in 10 (33%) women.

Blood loss was not measured, but on no occasion was the subjective loss so great as to warrant either blood transfusion or emergency uterine curettage.

RU 486 and RU 486 plus PG

There were no differences between these two groups in terms of the onset of abdominal cramps or vaginal bleeding. The median day of onset was 2 (range 0–4) and 3 (0–4) for pain, and 3 (1–6) and 3 (1–4) for bleeding, in the RU 486 alone and RU 486 + PG groups respectively. More women in the RU 486 + PG treatment group requested analgesia than in the RU 486 only treatment group (47% compared with 25%), although the difference was not statistically significant ($P=0{\cdot}09$). Only 3 (16%) women, all of whom were in the RU 486 + PG group, required pethidine or diamorphine, significantly fewer than in the group treated with PG alone, 53% of

Table 1. Characteristics of the women in the four treatment groups

	Treatment group			
	VA (*n*=28)	PG (*n*=30)	RU 486 (*n*=20)	RU 486+PG (*n*=19)
Age (years)	23 (19–39)	22 (18–38)	25 (17–41)	23 (17–38)
Height (cm)	168 (160–180)	168 (154–179)	168 (142–175)	165 (157–173)
Weight (kg)	59 (52–67)	55 (47–79)	64 (47–88)	61 (51–68)
Parous *n* (%)	5 (18%)	5 (17%)	5 (20%)	2 (11%)
Gestation (days)	49 (34–56)	49 (33–56)	47 (39–56)	47 (35–56)

Results are given as median (range) values except for the number of parous women.
VA, Vacuum aspiration; PG, gemeprost pessary.

whom required strong analgesic prescription ($P<0{\cdot}05$).

No serious complications were seen. Vomiting occurred in one woman before treatment with RU 486 alone and in three before they received the combined therapy. During therapy the number of women with vomiting was 3 of 20 (15%) in the RU 486 alone treatment group and 6 of 19 in the RU 486 + PG treatment group. There was no significant difference between the two groups, nor was there any difference before and after the administration of PG in the combined treatment group. Diarrhoea occurred on day 2 in one woman in the RU 486 alone group, and in one woman on day 3 in the RU 486 + PG group.

One woman in the RU 486 alone group needed an emergency uterine evacuation because of heavy bleeding 3 days after the cessation of treatment, and another one required blood transfusion because of heavy bleeding after uterine evacuation for treatment failure with RU 486 alone

Follow-up and success rates

Vaginal bleeding persisted for mean periods of 7 (range 1–25) days, 10 (1–17) days, 10 (6–29) days and 11 (5–34) days in the vacuum aspiration, PG alone, RU 486 alone and RU 486 + PG groups respectively. Complete abortion occurred in 27 of 28 (96%) women in the vacuum aspiration group, 29 of 30 (97%) in the PG alone group and and in 18 of 19 (95%) in the RU 486 + PG group. However, successful abortion was only achieved in 12 of 20 (60%) of those women treated with RU 486 alone ($P=0{\cdot}02$). The fate of those patients requiring uterine evacuation is shown in Fig. 1.

Discussion

The establishment of a medical approach to the termination of early pregnancy demands a success rate approaching that of vacuum aspiration and a low incidence of adverse effects. In addition, the method must be acceptable to both the woman seeking abortion and the provider of health care.

This study has confirmed the efficacy of gemeprost pessaries alone in the induction of early abortion (Smith & Baird 1980), although gastrointestinal side-effects occurred in 20–35%. A similar success rate was also obtained in those women treated with the combination of RU 486 and gemeprost, but although diarrhoea only occurred in one woman, 6 (32%) women experienced vomiting despite the reduced dose of prostaglandin. The women treated with RU 486 alone had a similar frequency of gastrointestinal

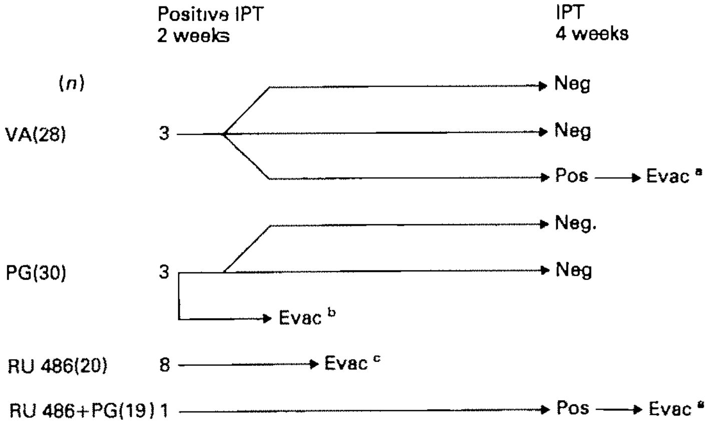

Fig. 1. Treatment failures The fate of each individual with a positive pregnancy test (IPT) 2 weeks following treatment is shown (a) Curettage revealed necrotic decidua but no villi, the IPT was weakly positive; (b) uterine evacuation at 2 weeks for ongoing pregnancy, (c) uterine evacuation at 2 weeks based on ultrasound—ongoing pregnancy (5), incomplete abortion (3)

VA, Vacuum aspiration, PG, gemeprost pessary.

upsets, but the 60% rate of complete abortion in this group was significantly lower than that in the other three treatment groups. Although diarrhoea is a more specific prostaglandin-associated side-effect, nausea and vomiting are common symptoms in early pregnancy; in the present study vomiting occurred in four women before treatment with RU 486 or RU 486 + PG, and medical treatment was discontinued in one patient due to severe nausea and vomiting prior to RU 486 administration. It may be that further reduction in the frequency of these side-effects will require specific anti-emetic premedication.

A complete abortion rate of 85% has recently been reported using RU 486 alone in varying doses to terminate early pregnancy within 10 days of the missed period (Couzinet *et al.* 1986). The findings of the present study are in keeping with previous work demonstrating a 60% complete abortion rate with RU 486 alone (Kovacs *et al.* 1984), but a success rate approaching 100% using the antiprogestogen in combination with prostaglandin (Swahn *et al.* 1985). Although the anti-progesterone action mechanism of RU 486 may induce uterine contractility by stimulating endometrial prostaglandin synthesis (Kelly *et al.* 1986), augmentation with endogenous prostanoids appears beneficial for rapid complete uterine evacuation.

Acute haemorrhage necessitating emergency curettage has been reported following treatment with RU 486 alone (Kovacs *et al.* 1984), as has a subjective increase in bleeding associated with a fall in haemoglobin concentration (Couzinet *et al.* 1986). In the present study although one woman required emergency curettage, objectively assessed blood loss in a further 24 women revealed no difference between the RU 486 and RU 486 + PG groups (Cameron *et al.* 1986). The degree of blood loss was similar to that reported previously after early abortion with either gemeprost pessaries or vacuum aspiration (Smith & Baird 1980), and was equivalent to the expected menstrual loss during a heavy period (Fraser *et al.* 1981).

Analgesic requirements were greater in those women treated with gemeprost pessaries alone than in those treated first with RU 486 before receiving the PG pessary. It seems likely that the five-fold reduction in the dose of the PG results in less severe contraction of the myometrium and gastrointestinal tract. Pretreatment with the antigestogen may also have induced a degree of cervical dilatation as well as sensitizing the myometrium to PG.

The diagnosis of treatment success was made at the 2-week follow-up appointment, based on clinical assessment together with ultrasound and endocrine assessment. But, it should be noted, that as a result of its long half-life, an elevated hCG concentration at this stage need not necessarily be indicative of incomplete abortion (Fig. 1).

In conclusion, the use of gemeprost pessaries alone, or in combination with RU 486, offers an effective alternative to surgery for early abortion, although the higher dose of prostaglandin is associated with an increased frequency of diarrhoea, and more painful uterine contractions. However, such treatment must be administered under close medical supervision both to detect the small number of treatment failures at an early stage, and also to diagnose ectopic pregnancy, which may not be evident at the start of drug administration (Kovacs *et al.* 1984). Further studies are required not only to determine the optimal dose regimen and duration of treatment with combinations such as RU 486 plus prostaglandin, but also to assess their effects in delaying subsequent ovulation, which may offer a major constraint to the use of these medical agents on a regular basis for fertility control (Baird & Cameron 1985; Hodgen 1985).

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References

Baird, D T. & Cameron, I. T. (1985) Menstrual induction: surgery versus prostaglandins. In *Abortion Medical Progress and Social Implications* (Ciba Foundation Symposium 115) John Wiley & Sons Ltd, London, pp 178-191.

Bygdeman, M , Green, K., Lundstrom, V., Ramadan, M., Fokiou, S & Bergstrom, S. (1976) Induction of abortion by vaginal administration of 15 (S) 15-methyl prostaglandin $F_{2\alpha}$ methyl ester. A comparison of two delivery systems. *Prostaglandins* **12** **(Suppl.)**, 27-51.

Bygdeman, M. & Green, K. (1979) Menstrual regulation· medical techniques In *Pregnancy Termina-*

tion—Procedures, Safety and New Developments (Zatuchni, G I., Sciarra, J J & Speidel, J. J , eds), Harper & Row, Philadelphia, pp 69-77.

Bygdeman, M , Bremme, K , Christensen, N., Lundstrom, V & Green, K. (1980) A comparison of two stable prostaglandin E analogues for termination of early pregnancy and for cervical dilatation *Contraception* **22,** 471-483

Cameron, I. T., Michie, E A. & Baird, D T (1986) Therapeutic abortion in early pregnancy with antiprogestogen RU 486 alone or in combination with prostaglandin analogue (cervagem) *Contraception* **34,** 459-468

Couzinet, B., Le Strat, N., Ulmann, A , Baulieu, E. E & Schaison, G (1986) Termination cf early pregnancy by progesterone antagonist RU 486 (mifepristone). *N Engl J Med* **315,** 1565-1570.

Csapo, A. I., Pulkkinen, M O & Kaihola, H L (1973) The effect of luteectomy-induced progesterone-withdrawal on the oxytocin and prostaglandin response of the first trimester pregnant human uterus *Prostaglandins* **4,** 421-429.

Csapo, A. I., Peskin, E. G , Pulkkinen, M., Laajoki, V , Kivikoski, A., Lampe, L , Godeny, S., Szeverenyi, M., Herczeg, J , Resch, B & Bacos, L. (1982) 'Menstrual induction' with sulprostone. *Prostaglandins* **24,** 657-665

Fraser, I. S., Pearse, C , Shearman, R. P., Elliott, P M., Mclveen, J & Markham, R. (1981) Efficacy of mefenamic acid in patients with a complaint of menorrhagia *Obstet Gynecol* **58,** 543-551.

Grimes, D. A. & Cates, W (1979) Complications from legally-induced abortions a review. *Obstet Gynecol Surv* **34,** 177-191

Healy, D. L & Fraser, H M (1985) The antiprogesterones are coming: menses induction, abortion, and labour? *Br Med J* **290,** 580-581

Hobson, B. M. (1968) Pregnancy diagnosis using Pregnosticon haemagglutination inhibition test *Br J Obstet Gynaecol* **75,** 718-723

Hodgen, G. D (1985) Pregnancy prevention by intravaginal delivery of a progesterone antagonist: RU 486 tampon for menstrual induction and absorption. *Fertil Steril* **44,** 263-267.

Karim, S M. M & Filshie, G M (1970) Therapeutic abortion using prostaglandin $F_{2\alpha}$ *Lancet* **i,** 157-159.

Karman, H & Potts, M. (1972) Very early abortion using syringe as vacuum source *Lancet* **i,** 1051-1052

Kelly, R W., Healy, D L , Cameron, M J., Cameron, I. T & Baird, D T (1986) The stimulation of prostaglandin production by two antiprogesterone steroids in human endometrial cells *J Clin Endocrinol Metab* **62,** 1116-1123

Kovacs, L , Sas, M , Resch, B. A., Ugoscai, G , Swahn, M L , Bygdeman, M. & Rowe, P J (1984) Termination of very early pregnancy by RU 486—an antiprogestational compound *Contraception* **29,** 399-410

Moscary, P & Csapo, A I (1975) Menstrual induction with $PGF_{2\alpha}$ and PGE_2 *Prostaglandins* **10,** 545-547

Office of Population Censuses and Surveys (1985) Abortion statistics. HMSO, London

Oshima, K., Matsumoto, K , Tsuda, T , Shibata, K & Hayashi, M. (1978) Decreased smooth muscle side effects with 16, 16 dimethyl-trans-Δ_2-PGE_1 methyl ester in Japanese monkey (Mac. Fusc Fusc.). *Prostaglandins* **15,** 473-483

Paintin, D. B (1985) Legal abortion in England and Wales. In *Abortion Medical Progress and Social Implications* (Ciba Foundation Symposium 115) John Wiley & Sons Ltd, London, pp. 4-12.

Rosen, A. S , Nystedt, L , Bygdeman, M & Lundstrom, V (1979) Acceptability of a non-surgical method to terminate very early pregnancy in comparison to vacuum aspiration. *Contraception* **19,** 107-117.

Smith, S K. & Baird, D. T. (1980) The use of 16, 16-dimethyl-trans-Δ_2- PGE_1 methyl ester (ONO 802) vaginal suppositories for the termination of early pregnancy A comparative study. *Br J Obstet Gynaecol* **87,** 712-717

Swahn, M. L , Cekan, S , Wang, G., Lundstrom, V & Bygdeman, M. (1985) Pharmacokinetic and clinical studies of RU 486 and human fertility regulation In *The Antiprogestin Steroid RU 486 and Human Fertility Control* (Baulieu, E. E. & Segal, S. J., eds), Plenum Press, New York, pp. 249-258

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Preterm caesarean section

SHEENA B. PINION, JAMES MOWAT

Summary. A retrospective study of 1921 caesarean sections at Rutherglen Maternity Hospital in Glasgow during the years 1979–1983, inclusive, showed that 229 (12%) were performed at less than 37 weeks gestation. Of these 229 preterm caesarean sections 41% were elective, 21% were for antepartum haemorrhage and 38% took place during labour. Of the 254 babies born 18 (7%) died in the neonatal period. These deaths comprised 31% of all neonatal deaths during the study period in this hospital. The neonatal death rate was 70% for babies weighing <1000 g (7 of 10) and 23% for babies weighing 1000–1500 g (6 of 26), but only 3% for babies heavier than this (7 of 217). Of the 75 women with a subsequent pregnancy after the preterm caesarean section 56% were again delivered by caesarean section. In view of the maternal morbidity associated with caesarean section and the poor neonatal outcome at birthweights of <1500 g, the use of operative delivery for very low birthweight infants deserves further scrutiny.

There has been much recent debate about the rise in the caesarean section rate and concern has been expressed in both the lay and medical press.

Recent advances in the neonatal care and long-term survival of preterm and growth-retarded babies has led to an increase in the number of preterm caesarean sections, whether 'elective' in the maternal or fetal interest, or to avoid the stress of vaginal birth for a compromised fetus.

The abdominal route does not, however, guarantee an easy delivery If the lower segment is unformed, a vertical incision in the uterus may be necessary. Subsequent pregnancies will be affected, with the risks of scar dehiscence and repeat operations, which may be greater than in women who have had a caesarean section at term

Subjects and methods

The case records of all patients having a preterm caesarean section (at less than 37 completed weeks from the last menstrual period) at Rutherglen Maternity Hospital in Glasgow during the period 1979–1983, inclusive, were studied. The indication for caesarean section, whether it was elective or in labour, the gestation and neonatal outcome were noted. The subgroup of women who had a subsequent pregnancy and delivery at Rutherglen (to the present date) was also analysed, to determine the proportion that required a repeat caesarean section and the indication. Any serious complication such as scar dehiscence, rupture or caesarean hysterectomy was noted.

Results

During the years 1979–1983 inclusive, 1921 patients were delivered by caesarean section and 229 (12%) of these were preterm at <37 completed weeks gestation. During this period neither the overall caesarean section rate nor the

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Rutherglen Maternity Hospital, 120 Stonelaw Road, Rutherglen, Glasgow G73 2PG
SHEENA B. PINION *Registrar in Obstetrics*
JAMES MOWAT *Consultant Obstetrician*

Correspondence: Dr S. Pinion, Registrar in Obstetrics, Stirling Royal Infirmary, Stirling, Scotland

Table 1. Indications for preterm caesarean section, 1979–1983

Indication	No. of patients
Elective before labour	
Pre-eclampsia	45*
Intrauterine growth retardation	31
Twins	8
Miscellaneous	9
Antepartum haemorrhage	
Placental abruption	22
Placenta praevia	26
Emergency in labour	
Breech	24
Fetal distress	15
Twins	12
Failure to progress	10
Previous LSCS	7
Transverse lie	6
Cord prolapse	5
Prematurity only	3
Miscellaneous	6

* One patient had eclampsia

proportion of preterm sections changed significantly.

Of the 229 patients, 56% were primigravidae (or had only had a previous first or second trimester abortion) and 44% had had a previous delivery; 27 patients (12%) had had a previous caesarean section, 6 of these had also had a vaginal delivery (3%).

Indications

In seven patients, elective caesarean section was planned, but preterm labour led to early delivery. The other main indications were pre-eclampsia, intrauterine growth retardation, antepartum haemorrhage and breech presentation (Table 1). Of the 229 preterm caesarean sections 93 (41%) were 'elective' before labour, 48 (21%) were for antepartum haemorrhage (placental abruption or placenta praevia) and 88 (38%) took place after the onset of preterm labour.

Two deliveries were by classical caesarean section and three by inverted T incisions, the remainder by lower segment operations. One section was for abdominal pain and presumed scar dehiscence from a previous delivery but this was found not to be the case.

There were no maternal deaths.

Neonatal outcome

Of the 254 babies born, two (including one twin) were stillbirths. There were 18 neonatal deaths, eight were due to fetal abnormality. The birthweights are shown in Table 2. Seven of the deaths occurred in babies weighing <1000 g (only one was due to fetal abnormality). Both of the neonatal deaths in babies weighing >2500 g were due to abnormality.

In addition, one baby has congenital heart disease, one had bilateral lower limb amputations after problems with an umbilical catheter, and one, born by caesarean section for placental abruption, is known to be mentally retarded.

During the period of the study there were 60 stillbirths and 58 neonatal deaths in the hospital so that 31% of the neonatal deaths occurred in babies born by preterm caesarean section.

Breech presentation

Of the 24 babies born by caesarean section for breech presentation one weighed between 1000 and 1499 g, three weighed >3000 g and the rest weighed between 1500 and 2999 g. In this group two neonatal deaths were due to fetal abnormality.

One of the sections for cord prolapse occurred in a breech presentation. Two abruptions occurred during external cephalic version for breech.

Subsequent pregnancies

Of the 229 women, 75 had a total of 90 pregnancies (booked at Rutherglen Maternity Hospital) after their first preterm section, to the present date. Of these 90 pregnancies 39 (43%) ended in

Table 2. Birthweights of livebirths and stillbirths/neonatal deaths delivered by preterm caesarean section, 1979–1983

Birthweight (g)	No. of babies	No. of stillbirths/ neonatal deaths
<1000	10	7 (70%)
1000–1499	26	6 (23%)
1500–1999	63	3 (5%)
2000–2499	81	2 (2%)
2500–2999	60	1 (2%)
3000–3499	11	1 (9%)
3500–3999	2	0
Total	253	20 (8%)

Table 3. Indication for first and subsequent caesarean section in patients requiring repeat section

Indication	First section ($n = 42$)	Second section ($n = 42$)
Elective section	28	28
Antepartum haemorrhage	9	6
Emergency section in labour	5	8

vaginal delivery (spontaneous or forceps), 32 (36%) were delivered by elective repeat caesarean sections and 19 (21%) by emergency caesarean section in labour. In only nine patients was the indication for the second section the same as that for the first. In total, 42 patients (56%) had a subsequent caesarean section. The indications for the first and second caesarean section are shown in Table 3.

Two patients had dehiscence of the previous uterine scar, one of them required hysterectomy and the other was found at caesarean section. One other patient had a hysterectomy for postpartum haemorrhage.

Two women had vaginal deliveries at less than 26 weeks gestation, two others were planned to be delivered by elective section, but they progressed in labour and were delivered vaginally.

In 59 of the 75 women the index caesarean section was their first delivery, 34 (58%) of them had a subsequent delivery by caesarean section and 25 (42%) had a vaginal delivery. Thirteen women had had a previous vaginal delivery before the index section, 5 (38%) had a repeat caesarean section and 8 (61%) a further vaginal delivery in the subsequent pregnancy. Three patients had had a previous caesarean section and all of these were delivered by repeat section.

There were no classical sections and no T incisions. There were no maternal deaths.

Discussion

The proportion of preterm sections in this study (12%) is similar to that found by McIlwaine *et al* (1985) for the whole of Scotland. A large number of these operations (41%) were 'elective' procedures. Although caesarean section is now a fairly 'safe' procedure, it does carry all the risks of major surgery, with a mortality of 2–11 times that of vaginal delivery (Petitti 1985) and a significant morbidity (Haddad 1978).

A large proportion (56%) had a subsequent caesarean section. This must therefore be included in the maternal morbidity arising from preterm caesarean section. Many authors (Graham 1984; Meier & Porreco 1982; Paul *et al.* 1985; McGarry 1969, Yudkin & Redman 1986) have studied the mode of delivery in patients who have had a previous section, but none has specifically looked at the outcome of pregnancies following preterm section. In fact, the frequency of scar dehiscence was low in these patients, and similar to that for caesarean sections at term (0–4%). Unless there are other factors prohibiting vaginal delivery, there is no contraindication to a 'trial of labour' in future pregnancies.

Survival in babies weighing <1500 g was poor, and 31% of all neonatal deaths in this period occurred in babies born by preterm section. Other authors agree that increasing the caesarean section rate does not automatically decrease perinatal mortality. Liu & Fairweather (1981) and Westgren *et al.* (1985) found no significant difference in outcome for vertex presentation. O'Driscoll & Foley (1983) have shown that a decrease in perinatal mortality can occur to the same degree without a concomitant increase in the caesarean section rate.

Macnaughton (1981) suggested that preterm induction of labour, with proper intrapartum monitoring, was justified where the presentation was cephalic and the fetal weight >1500 g.

In the present study, 20 of 24 babies born by caesarean section for breech presentation weighed between 1500 and 2999 g. In a review of preterm breech delivery Bodmer *et al.* (1986) found that caesarean section did not decrease the frequency of neonatal depression or mortality, except in babies weighing <1000 g, where head entrapment by the cervix was responsible for seven deaths. Crowley & Hawkins (1980) reviewed the literature on vaginal versus abdominal delivery in breech presentation and concluded that survival was not affected by mode of delivery in babies weighing between 1500 and 2500 g. There was a significant advantage in caesarean section for babies weighing between 1000 and 1500 g, but for babies weighing <1000 g outcome was generally poor.

By allowing selective vaginal breech delivery and considering preterm induction of labour in the first instance, the caesarean section rate with its attendant morbidity could be decreased, with little effect on neonatal mortality.

References

Bodmer, B., Benjamin, A., McLean, F. H. & Usher, R N (1986) Has use of caesarean section reduced the risks of delivery in the preterm breech presentation? *Am J Obstet Gynecol* **154,** 244-250.

Crowley, P. & Hawkins, D. S. (1980) Premature breech delivery—the caesarean section debate. *J Obstet Gynecol* **1,** 2-6

Graham, A. R (1984) Trial of labour following previous caesarean section. *Am J Obstet Gynecol* **149,** 35-45.

Haddad, H. & Lundy, L. E. (1978) Changing indications for cesarean section: A 38-year experience at a community hospital. *Obstet Gynecol* **51,** 133-137

Liu, D. T. Y. & Fairweather, D. V. I. (1981) The management of preterm labour In *Preterm Labour* (Elder, M. G. & Hendricks, C. H., eds), Butterworths, London, pp. 231-258.

McGarry, J. A (1969) The management of patients previously delivered by caesarean section *J Obstet Gynaecol Br Commonw* **76,** 137-143.

McIlwaine, G. M., Cole, S. K. & Macnaughton, M. C. (1985) The rising caesarean section rate—a matter of concern? *Health Bull (Edinb)* **43,** 301-305.

Mcnaughton, M. C. (1981) Induction of preterm labour—why, when and how? In *Preterm Labour* (Elder, M. G & Hendricks, C. H., eds), Butterworths, London, p. 196

Meier, P & Porreco, R. (1982) Trial of labour following caesarean section a two year experience. *Am J Obstet Gynecol* **144,** 671-678.

O'Driscoll, K & Foley, M. (1983) Correlation of decrease in perinatal mortality and increase in caesarean section rate *Obstet Gynecol* **61,** 1-5.

Paul, R H , Phelan, J P. & Yeh, S (1985) Trial of labour in the patient with a prior caesarean birth *Am J Obstet Gynecol* **151,** 297-304.

Petitti, D. B. (1985) Maternal mortality and morbidity in caesarean section. *Clin Obstet Gynecol* **28,** 763-769.

Westgren, M. & Paul, R. H (1985) Delivery of the low birthweight infant by caesarean section. *Clin Obstet Gynecol* **28,** 752-762.

Yudkin, P L & Redman, C. W G. (1986) Caesarean section dissected 1978–83 *Br J Obstet Gynaecol* **93,** 135-144.

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Complement factors in fetal and maternal blood and amniotic fluid during the second trimester of normal pregnancy

I. STABILE, K. H. NICOLAIDES, A. BACH, B. TEISNER,
C. RODECK, J. G. WESTERGAARD, J. G. GRUDZINSKAS

Summary. Complement factors (C3, C4, C5; Factors B, H and I) were measured in maternal and fetal serum and amniotic fluid obtained from 55 women with singleton pregnancy undergoing diagnostic fetoscopy at 15 to 28 weeks gestation. Maternal serum levels were consistently 10 times higher than fetal levels which in turn were 10 times higher than levels in amniotic fluid. Spearman rank correlation analysis at weeks 20 to 22 ($n = 20$) revealed a statistically significant correlation between maternal and fetal levels of C3 and Factors B and I, and between maternal and amniotic fluid levels of Factors B and I. A significant increase in fetal levels of C3, C4 and Factor H, and in amniotic fluid levels of C3 and Factor B was seen in relation to advancing gestational age. These differences were not seen in maternal serum during the short interval of pregnancy studied. These data confirm earlier assumptions of fetal synthesis of complement factors, and provide normal reference ranges of complement factors in fetal blood and amniotic fluid.

The complement group of proteins is regarded as the principal effector of the humoral immunological system and is involved in mediating the inflammatory response and the defence against microbial infections. Inherited and acquired deficiencies of the complement system are associated with diseases such as recurrent severe infections (Teisner *et al.* 1984) and immunocomplex mediated syndromes (Schifferly & Peters 1983).

The evidence of complement synthesis by the fetus has hitherto been based on in-vitro studies on aborted fetal material in the first and second trimesters of pregnancy. By incubating fetal tissues in media containing labelled amino acids, Adinolfi (1977) demonstrated *de novo* synthesis of C3 and C4 by the liver, peritoneal and alveolar cells. Another approach has been the comparison between maternal and fetal blood levels of complement factors in samples obtained at

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Academic Unit of Obstetrics and Gynaecology, The London Hospital Medical College, London, UK
I STABILE
J. G. GRUDZINSKAS

Harris Birthright Research Centre for Fetal Medicine, King's College Hospital, London, UK
K. H. NICOLAIDES
C. RODECK

Institute of Medical Microbiology, Odense University Hospital, Odense, Denmark
A. BACH (died 22 April 1987)
B. TEISNER

Department of Obstetrics and Gynecology, Odense University Medical School, Odense, Denmark
J G WESTERGAARD

Correspondence: Professor J G. Grudzinskas, Department of Obstetrics and Gynaecology, 4th Floor, Holland Wing, The London Hospital, Whitechapel, London E1 1BB

the time of delivery (Adinolfi & Beck 1976). The lack of correlation between maternal and fetal levels, estimated by specific antibodies or by haemolytic functional assays, has been taken as indirect evidence of fetal synthesis.

The introduction of invasive techniques for fetal blood sampling such as fetoscopy (Rodeck & Campbell 1978; Nicolaides & Rodeck 1984) and cordocentesis (Nicolaides *et al.* 1986) has provided us with the opportunity to directly examine and compare the fetal, amniotic fluid and maternal levels of some of the complement factors and regulatory proteins.

Subjects and methods

A cross-sectional study was undertaken in 55 women with retrospectively defined normal singleton pregnancies, who were undergoing diagnostic fetoscopy or cordocentesis for the exclusion of haematological disorders and chromosomal defects (Nicolaides & Rodeck 1984), from 15 to 28 weeks gestation. The gestational age was determined from the first day of the last menstrual period and confirmed by ultrasonography.

Fetal (0·5 ml) and maternal (5·0 ml) blood samples as well as amniotic fluid (5·0 ml) were collected from each patient. The plasma was separated by centrifugation at 2000 r/min for 10 min and stored at −20°C until measured for the various complement components. The amniotic fluid was centrifuged immediately after collection and stored as above.

Restricted by the availability of fetal blood, we studied a component of the classical pathway (C4), the alternative pathway (Factor B), C3 situated at the junction of these two pathways, C5 of the membrane attack complex as well as two regulatory proteins (Factors H and I), in the second trimester of normal pregnancy.

Complement measurements

The sera and amniotic fluid were assayed by rocket immunoelectrophoresis using 1% agarose gel in 0·02 M tris barbital buffer at pH 8·6. The gel contained antibodies to the various complement components at different concentrations (anti-C4, see Folkersen *et al.* 1985; anti-C3, anti-Factor B, anti-C5 from Dakopatts, Denmark). Na_2 EDTA was added to each sample to achieve a final concentration of 10 mM. Aliquots (15μl) of matched fetal, maternal and amniotic fluid samples were applied to the same plate. The maternal samples were diluted 10-fold, except for Factor I quantification, where all samples were applied undiluted to the plate. The electrophoresis was run at 2·5 V/cm for 18 h. After staining, the precipitation areas were enlarged by projection and quantification of the complement components determined with reference to the standard curve obtained from a dilution series based on pooled sera from 50 apparently normal healthy non-pregnant adults. Measurements are expressed in arbitrary units (U) in relation to this pool (Rasmussen *et al.* 1986). These procedures are described in detail elsewhere (Laurell 1966).

Statistical analysis

The data were analysed (Sperry Univac-1100) using the statistical package for Social Sciences (SPSS). Since the complement factors showed a non-Gaussian distribution the data were $\log_{10}$-transformed (Log_{10}) for analysis. The mean values were determined and Spearman rank correlation analysis was performed to examine the association between gestational age and the levels within and between each compartment.

Results

The levels of the complement factors and regulatory proteins studied in the fetal and maternal circulations, and amniotic fluid are summarized in Fig. 1. After logarithmic transformation, the mean and standard deviation for each of the complement factors in the three compartments studied are shown in Table 1.

It was possible to quantify all the complement factors in all the maternal and fetal sera studied. However, since levels in amniotic fluid were below the detection limit of the assay in a significant number of samples for C5 (52/55) and Factor H (43/55), this analysis was performed for C3, C4, Factors B and I only.

Maternal levels were generally 10 times higher than fetal levels which, in turn, were 10 times higher than levels in the amniotic fluid.

The relations of levels of the complement factors to gestational age are shown in Table 2.

Spearman rank correlation analysis revealed a significant positive correlation ($P<0·001$) in fetal levels of C3, C4 and Factor H with advancing pregnancy. Maternal complement levels did not appear to be correlated with gestational age

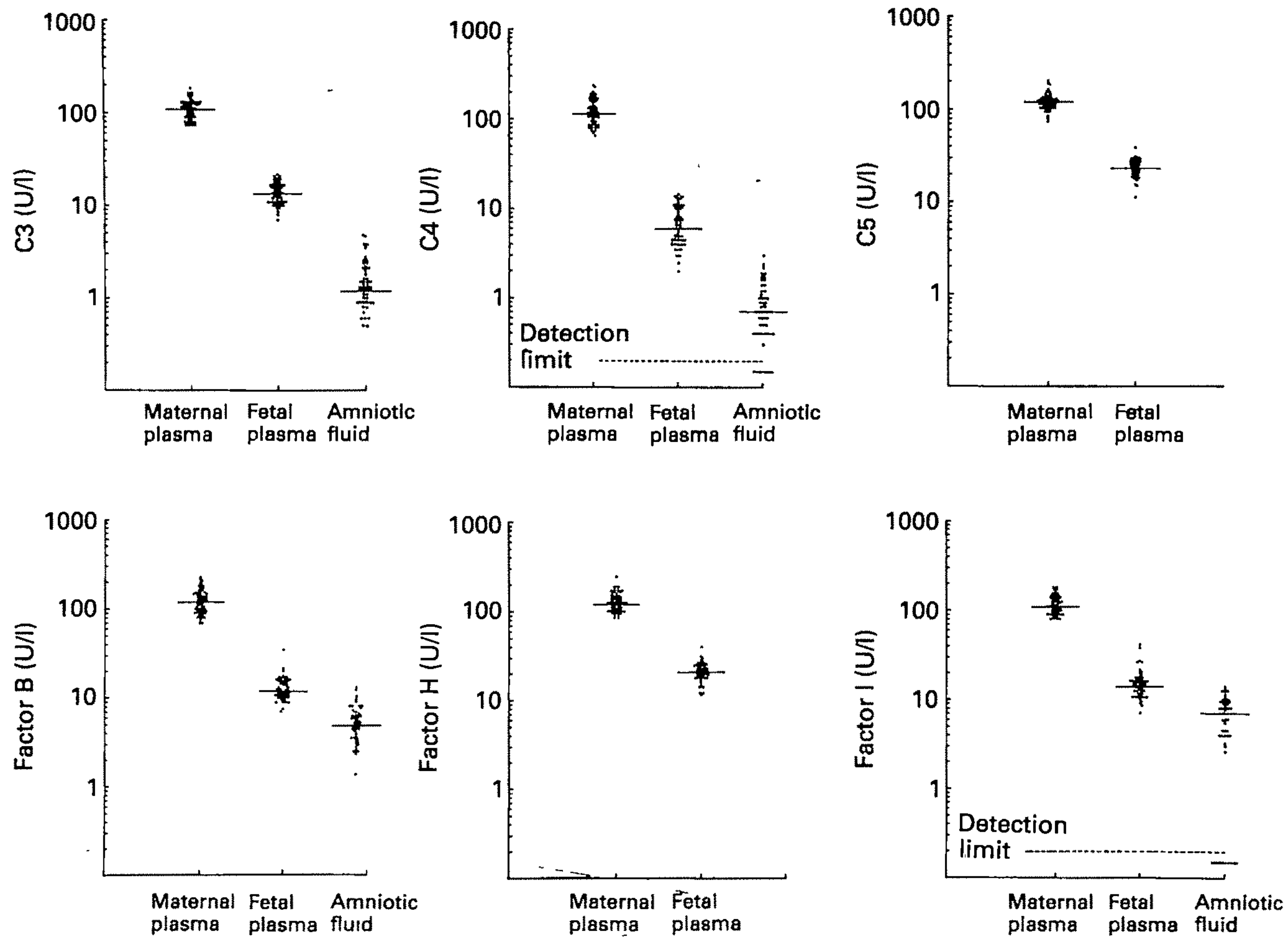

Fig. 1. Levels of C3, C4, C5, Factor B, Factor H, and Factor I in the maternal and fetal circulation, and amniotic fluid. The horizontal bars represent the mean values after log transformation.

Table 1. Circulating and amniotic fluid levels of complement factors during the second trimester of normal pregnancy

Component	Maternal	Fetal	Amniotic fluid
C3	2·06 (0·11)	1·10 (0·12)	0·13 (0·04)
C4	2·09 (0·15)	0·83 (0·21)	0·09 (0·03)
C5	2·09 (0·09)	1·37 (0·09)	—
Factor B	2·08 (0·13)	1·09 (0·12)	0·72 (0·19)
Factor H	2·10 (0·10)	1·32 (0·11)	—
Factor I	2·06 (0·10)	1·17 (0·15)	0·85 (0·20)

Results are mean (SD) values after logarithmic transformation.

Table 2. Spearman rank correlation analysis (*r*) of circulating and amniotic fluid levels of complement factors in 55 women at 15–28 weeks gestation in relation to gestational age

	Maternal		Fetal		Amniotic fluid	
Component	(*r*)	(*P* value)	(*r*)	(*P* value)	(*r*)	(*P* value)
C3	−0·13	NS	0·57	<0·0001	0·53	<0·001
C4	−0·12	NS	0·52	<0·0001	0·17	NS
C5	0·15	NS	0·21	NS	—	—
Factor B	−0·21	NS	0·02	NS	0·28	<0·02
Factor H	0·03	NS	0·39	<0·005	—	—
Factor I	0·06	NS	0·21	NS	0·08	NS

Table 3. Spearman rank correlation analysis (*r*) between maternal, fetal and amniotic fluid levels of complement factors studied in 20 women at 20–22 weeks gestation

	Maternal/fetal		Maternal/amniotic fluid		Fetal/amniotic fluid	
Component	(*r*)	(*P* value)	(*r*)	(*P* value)	(*r*)	(*P* value)
C3	0·46	0·02	0·30	0·09	0·14	NS
C4	0·08	NS	0·21	NS	0·64	0·002
C5	0·34	NS	—	—	—	—
Factor B	0·41	0·04	0·51	0·009	0·15	NS
Factor H	0·26	NS	—	—	—	—
Factor I	0·51	0·01	0·40	0·048	0·31	NS

in the short interval studied. Within the amniotic fluid only C3 and Factor B levels increased with advancing pregnancy. The correlation between the different compartments could only be examined in a narrow gestational age range (20–22 weeks) in 20 women, in order to avoid the effect of advancing gestation. The results of correlation analysis of the concentrations of the complement factors between maternal and fetal plasma, maternal plasma and amniotic fluid, and fetal plasma and amniotic fluid are shown in Table 3.

A significant correlation ($P<0{\cdot}05$) was observed between maternal and fetal plasma levels of C3, Factor B and Factor I; between maternal plasma and amniotic fluid levels of Factors B and I, and between fetal plasma and amniotic fluid levels of C4.

Discussion

This study was initiated to examine the relation of the levels of complement factors and regulatory proteins between the maternal and fetal circulations and amniotic fluid in the second trimester of pregnancies which continued normally to term.

Maternal levels of these factors were consistently higher than those seen in the fetal circulation which in turn were higher than in the amniotic fluid in matched samples. These data may be used as evidence of independent fetal synthesis of these substances. Indeed, with increasing gestation, fetal levels of C3, C4 and Factor H are higher, implying independent synthesis of complement factors by the fetus. This is further supported by the apparent lack of increase in levels of these factors in matched maternal blood samples. However, having eliminated the possible effect of gestational age, we still observed a statistically significant correlation between maternal and fetal blood levels of C3 and Factors I and B in maternal and fetal blood. It is therefore possible that diffusion from the maternal circulation to the amniotic fluid or fetal compartment may be responsible, at least in part, for our findings. Nevertheless, the fetus of a mother with high complement levels may itself tend to have elevated levels. Examination of fetal, maternal and paternal allotypes of these factors could clarify this question which is important in the prenatal diagnosis of hereditary deficiency states. Since hereditary complement deficiencies are rare (Rasmussen *et al.* 1986), the potential value of these estimations is limited to high-risk families previously identified as heterozygous for these deficiencies, although depressed levels in heterozygous fetuses may give falsely positive results.

This study has provided confirmatory evidence that complement components are produced at an early stage of fetal life and provided the basis for derivation of normal reference ranges of complement factors in fetal blood and amniotic fluid. These data may be useful in the prenatal diagnosis of immunodeficiency disorders in selected high-risk families, as well as in the diagnosis and management of fetal and neonatal infection.

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Dr Annelise Bach (Faculty Dean) sadly passed away after a short illness on 22 April 1987.

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References

Adinolfi, M. (1977) Human complement onset and site of synthesis during fetal life *Am J Dis Child* **131**, 1015-1023.

Adinolfi, M & Beck, S E. (1976) Human complement—C7 and C9—in fetal and newborn sera *Arch Dis Child* **50**, 562-564

Folkersen, J , Teisner, B., Petersen, N E , Sim, R. B & Jessen, E (1985) Preparation of antibodies against the fourth complement component (C4) and the development of a direct electroimmunoassay for quantification of C4d *J Clin Lab Immunol* **16**, 163-167

Laurell, L B. (1966) Quantitative estimation of proteins by electrophoresis in agarose gel containing antibodies *Anal Biochem* **15**, 45-52

Nicolaides, K. H & Rodeck, C H (1984) Fetoscopy *Br J Hosp Med* **35**, 396-405

Nicolaides, K. H , Soothill, P. W , Rodeck, C H & Campbell, S (1986) Ultrasound guided sampling of the umbilical cord and placental blood sampling to assess fetal well-being *Lancet* **i**, 1065-1067

Rasmussen, J M , Teisner, B , Brandslund, I & Svehag, S E (1986) A family with complement factor I deficiency. *Scand J Immunol* **23**, 711-715

Rodeck, C H & Campbell, S (1978) Sampling pure fetal blood by fetoscopy in the second trimester of pregnancy *Br Med J* **ii**, 728-730

Schifferly, J. A. & Peters, D K (1983) Complement, the immune complex lattice and the pathophysiology of complement deficiency syndromes. *Lancet* **ii**, 957-959

Teisner, B , Brandslund, I., Folkersen, J , Poulsen, L O. & Svehag, S. E (1984) Factor I deficiency and C3 nephritic factor· immunochemical findings and association with Neisseria meningitidis infection in two patients. *Scand J Immunol* **20**, 291-297.

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Amoxycillin-clavulanic acid (Augmentin) versus metronidazole as prophylaxis in hysterectomy: a prospective, randomized clinical trial

E. M. BROWN, J. DEPARES, A. A. ROBERTSON, S. JONES, A. B. HUGHES, E. C. COLES, J. R. MORGAN

Summary. In order to determine the most effective regimen for the prevention of infection after elective hysterectomy, 300 patients were randomly assigned to receive three perioperative doses of either amoxycillin-clavulanic acid (1·2 g intravenous) or metronidazole (1 g suppository). Of the 280 patients who were assessable 138 were given amoxycillin-clavulanic acid and 142 received metronidazole; 268 underwent abdominal hysterectomy and 12 had vaginal hysterectomy. Patients in the amoxycillin-clavulanic acid group had significantly less infectious morbidity (13 8%) than those in the metronidazole group (33·1%). There were also statistically significant differences in favour of amoxycillin-clavulanic acid with respect to operative site infection, duration of hospital stay, need for postoperative antimicrobials, and surgery for operative site infection. But for one isolate of *Bacteroides fragilis*, all pathogens isolated from wound infections in the metronidazole group were aerobes. No anaerobes were isolated from patients in the amoxycillin-clavulanic acid group. The results suggest that prophylaxis for hysterectomy should consist of an agent, or combination of agents, with activity against both aerobic and anaerobic bacteria. Amoxycillin-clavulanic acid fulfils this criterion and appears to be effective and safe.

Infections following elective major gynaecological surgery such as abdominal and vaginal hysterectomy are common and represent a significant source of postoperative morbidity. The most important of these infections are inevitably those at the operative site since gynaecological surgery is often performed through a grossly contaminated field and it is the mixed aerobic/anaerobic bacterial flora of the lower genital tract that serves as a reservoir for most of the pathogens associated with postoperative sepsis (Blackmore *et al.* 1981). Some workers have demonstrated a significant decrease in infection following the prophylactic use of metronidazole with its specific activity against anaerobic bacteria (Study Group 1974; Appelbaum *et al.* 1978; Jackson *et al.* 1979, Hamod *et al.* 1980; Poulsen *et al* 1984), the

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University Hospital of Wales, Heath Park, Cardiff CF4 4XW
Department of Medical Microbiology
E M. BROWN
J R. MORGAN
Department of Obstetrics and Gynaecology
J DEPARES
A. A ROBERTSON
S. JONES
A. B HUGHES
Department of Medical Statistics
E. C. COLES

Correspondence: E M. Brown, Pathology Department, Frenchay Hospital, Bristol BS16 1LE

predominant component of the local microflora. However, most studies that have demonstrated the efficacy of antimicrobials in gynaecological surgery have used agents, principally first generation cephalosporins (Hirschmann & Inui 1980; Polk 1981), to which the commonly isolated, anaerobic, Gram-negative bacilli are frequently resistant. There is presently no acceptable explanation for this paradox. The recurrent question exists, therefore, as to whether it is necessary to administer an antimicrobial, or combination of antimicrobials, with activity against most of the potential pathogens in the vaginal flora, including obligate anaerobes, or whether prophylaxis can adequately be directed against anaerobic bacteria alone.

Augmentin is a formulation of amoxycillin and the beta-lactamase inhibitor, clavulanic acid. It has been shown to have a wide range of activity which embraces both Gram-positive and Gram-negative facultative organisms, as well as anaerobes, including *Bacteroides fragilis* (Neu & Fu 1978; Wise *et al.* 1978; Brown 1984). Amoxycillin-clavulanic acid, therefore, has the breadth of spectrum to allow it to be used alone as prophylaxis in gynaecological surgery. This study was undertaken to compare amoxycillin-clavulanic acid with metronidazole in preventing sepsis following hysterectomy and thereby to establish the nature of the most effective prophylactic regimen.

Patients and methods

Women admitted to Cardiff hospitals for elective abdominal or vaginal hysterectomy were included in the trial, provided none of the following exclusion criteria applied: a history of allergy to penicillins; exposure to antibiotics within 1 month of surgery; severe renal disease; signs of pre-existing infection; valvular heart disease requiring prophylaxis against bacterial endocarditis; or conditions predisposing to infection, such as diabetes mellitus, autoimmune disease, steroid therapy.

Patients were allocated to one of two prophylactic regimens by simple randomization, without prior stratification, using previously prepared, sealed envelopes. Patients in regimen 1 received amoxycillin-clavulanic acid, 1·2 g intravenously, following induction of anaesthesia and two additional doses at intervals of 8 h after the first, while those in regimen 2 received a metronidazole suppository (1 g) with the premedication and an additional suppository at 8 and 16 h after the first administration. A placebo group was not included because some of the gynaecologists participating in the trial were unwilling to permit their patients to undergo surgery without prophylaxis and because the aim of the study was to establish the most effective form of prophylaxis for hysterectomy, not the efficacy of prophylaxis itself.

After surgery, and until hospital discharge, each patient was assessed daily by a designated clinician for evidence of infection at the operative site, the urinary tract and the respiratory tract, as well as systemic or local drug reactions. As it was not possible in every instance to ensure that those assessing outcome were blinded to the group allocation of the patients, strict objective criteria for defining postoperative febrile morbidity and infection were adopted prospectively in order to reduce observer bias. Febrile morbidity was defined as an oral temperature of ≥38°C recorded on at least two successive occasions more than 6 h apart, excluding the first 24 h after surgery. Infectious morbidity referred to clinical or bacteriological evidence of one or more specific postoperative infections (e.g. abdominal wound infection, vaginal or pelvic infection, urinary or respiratory tract infection). Surgical wound infection described any wound which discharged, spontaneously or otherwise, purulent material with or without culture of a pathogen. Vaginal/pelvic infection was established by the presence of a purulent vaginal discharge or a pelvic mass with pain and tenderness. Urinary tract infection was diagnosed by the presence of ≥100 000 organisms/ml of urine (or catheter bacteriuria <100 000 organisms/ml). Respiratory tract infection was defined by the presence of cough with purulent sputum, physical or radiological signs consistent with pneumonia, or isolation of a heavy growth of pathogenic bacteria from sputum.

The duration of postoperative hospitalization, the postoperative use of antimicrobials for therapeutic reasons, and the number of patients requiring surgery for operative site infection were also recorded and used as indirect criteria of the efficacy of the prophylactic regimens.

Specimens of purulent material, urine, and sputum were collected as indicated by the patient's clinical condition. Vaginal cultures were obtained only in the presence of a purulent discharge. All specimens were examined by conventional bacteriological techniques and any pathogens were tested for susceptibility to the appropriate antimicrobials by a disc diffusion method.

All results were tabulated and statistical analyses were performed using the χ^2 test (with Yates' correction for 2 × 2 tables) and Student's *t*-test as appropriate.

Results

Over a period of 18 months 300 patients were entered into the study. This sample size was selected in order to give a power of 67% of detecting a difference in infection rate of 10 percentage points between the two groups (assuming an overall infection rate of approximately 15% and using the conventional alpha = 0·05 significance level). Twenty patients were later withdrawn for the following reasons: hysterectomy not performed as a result of intra-operative findings, including pelvic sepsis which was previously undiagnosed (eight patients; five in regimen 1, three in regimen 2); violations of protocol (10 patients; six in regimen 1, four in regimen 2); and loss of clinical data (two patients, one in each group) There were thus 12 patients withdrawn from regimen 1 and eight from regimen 2.

Of the 280 patients who were available for analysis, 268 underwent abdominal hysterectomy and 12 had vaginal hysterectomy. Of the 280 patients 138 received amoxycillin-clavulanic acid and 142 received metronidazole. Tables 1 and 2 list the demographic characteristics of the two groups and the factors that might be expected to influence the frequency of postoperative infectious morbidity. Operator status did not have a significant impact on patient outcome with respect to infectious ($\chi^2 = 0{\cdot}04$; d.f. = 3; $P>0{\cdot}5$) and febrile morbidity ($\chi^2 = 3{\cdot}26$; d.f. = 3; $0{\cdot}5>P>0{\cdot}2$).

Table 3 summarizes the rates and types of infection in the two groups of patients. No serious morbidity occurred in either group. Patients receiving amoxycillin-clavulanic acid had less infectious morbidity (13·8%) than those who received metronidazole (33·1%) and this difference was highly statistically significant ($P<0{\cdot}001$). There was also less febrile morbidity in regimen 1 but the difference was not statistically significant ($0{\cdot}2>P>0{\cdot}1$). Diagnosis of surgical wound infection (abdominal or vaginal/pelvic) was made in 3 of 138 patients (2·2%) in the amoxycillin-clavulanic acid group and in 16 of 142 patients (11·3%) in the metronidazole group ($P<0{\cdot}01$). There were no respiratory tract infections in regimen 1 and seven in regimen 2 ($P<0{\cdot}025$). A comparison of urinary tract infections indicated a higher incidence of bacteriuria in patients receiving metronidazole ($0{\cdot}1>P>0{\cdot}05$).

Indirect evidence of the efficacy of the prophylactic regimens, as indicated by mean duration of postoperative hospital stay, the number of patients requiring surgery (simple drainage) for postoperative wound sepsis, and the number of patients prescribed subsequent courses of antibiotics, is summarized in Table 4 For all three factors there were statistically significant differences in favour of amoxycillin-clavulanic acid. The antimicrobials administered most frequently for postoperative infectious morbidity were cephradine, ampicillin/amoxycillin, cotrimoxazole and metronidazole, which altogether accounted for 75% of the agents used for this purpose. Significant bacteriuria, representing 53% of all identifiable postoperative infections, was the commonest indication for treatment.

The organisms cultured from the sites of postoperative sepsis according to the type of infection are listed in Table 5. With the exception of one *Bacteroides fragilis* which was sensitive to metronidazole, all of the pathogens isolated from wound infections in patients in regimen 2 were aerobes. *Staphylococcus aureus*, which was grown from 11 of the 16 specimens of pus obtained from this group, was the predominant pathogen. No anaerobes were isolated from wound infections in patients in regimen 1.

There was a significant difference between the two groups with respect to the types of urinary isolates. In the metronidazole group *Escherichia coli* and *Streptococcus faecalis* were isolated most often and with the same frequency. The other organisms consisted of a variety of *Enterobacteriaceae* and one each of a group B beta haemolytic streptococcus and a diphtheroid. All nine urinary isolates in the amoxycillin-clavulanic acid group were identified as *E. coli*, only two of which were resistant to amoxycillin-clavulanic acid.

Two patients on amoxycillin-clavulanic acid developed an urticarial rash at 6 and 7 days respectively after administration of the drug. However, because of the long interval it was not possible to be certain that the two events were

Table 1. Demographic profile of the patient population

	Amoxycillin-clavulanic acid	Metronidazole
No. of patients	138	142
Age (years)		
mean (SD)	42·8 (9·3)	43·0 (10·1)
range	26–74	25–80
Weight (kg)		
mean (SD)	63·4 (10·9)	64·9 (12·1)
range	41·0–103·0	39·8–115·7
No. (%) of postmenopausal patients	14 (10)	13 (9)
Socio-economic class score*		
mean (SD)	4·3 (1·4)	4·6 (1·5)
No. (%) smoking ≥10 cigarettes per day	43 (31·2)	55 (38·7)
Operative procedure		
Abdominal hysterectomy	130	138
Vaginal hysterectomy	8	4
Operator status†		
Senior house officer	8	8
Registrar	26	43
Senior registrar	42	36
Consultant	62	55
Duration of surgery (min)		
mean (SD)	65·3 (23·9)	63·6 (18·8)
Operative blood loss (ml)		
mean (SD)	235·4 (159·5)	247·7 (188·6)
Indwelling urinary catheter		
No. (%) of patients	12 (8·7)	14 (9·9)
Use of drain		
No. (%) of patients	33 (23·9)	33 (23·2)

*Socio-economic class score I = 1, II = 2, IIINM = 3, IIIM = 4, IV = 5, V = 6, N/C = 7.
†No significant difference between the two groups ($\chi^2 = 5{\cdot}0$, d.f. = 3, $0{\cdot}2 > P > 0{\cdot}1$).

Table 2. Primary indication for hysterectomy based on pre-operative diagnosis

Indication	Amoxycillin-clavulanic acid	Metronidazole
Menstrual abnormality	98	97
Cervical dysplasia	5	10
Cervical carcinoma	5	2
Uterine dysplasia	0	1
Uterine carcinoma	3	6
Ovarian carcinoma	0	4
Prolapse	8	3
Fibroids	7	8
Pelvic pain	11	9
Other	1	2
Total	138	142

related. No adverse reactions were attributable to metronidazole.

Discussion

The reported prevalence of infectious morbidity associated with hysterectomy varies widely but rates as high as 56% have been reported after abdominal hysterectomy (Appelbaum *et al.* 1978) and up to 77·5% after vaginal hysterectomy (Goosenberg *et al.* 1969). Despite these figures the use of prophylactic antibiotics in gynaecological surgery remains a controversial

Table 3. Incidence of febrile morbidity, infectious morbidity and specific postoperative infection

	Amoxycillin clavulanic acid (n = 138)	Metronidazole (n = 142)			
	n (%)	n (%)	Relative risk 95% CI*	χ^2	P
Infectious morbidity	19 (13·8)	47 (33·1)	0·42 (0·25 to 0·66)	13·5	<0·001
Febrile morbidity	9 (6·5)	18 (12·7)	0·51 (0·23 to 1·08)	2·4	NS
Specific postoperative infection					
Operative site	3 (2·2)	16 (11·3)	0·19 (0·04 to 0·57)	7·8	<0·01
Abdominal	2 (1·4)	14 (9·9)	0·15 (0·02 to 0·52)	7·7	<0·01
Vaginal/pelvic	1 (0·7)	2 (1·4)	0·51 (0·02 to 5·46)	0·001	NS
Respiratory tract	0 (—)	7 (4·9)	0·00	5·1	<0·025
Urinary tract	9 (6·5)	20 (14·1)	0·46 (0·21 to 0·95)	3·5	NS

NS, Not significant.

*Confidence interval (CI) calculated according to Bailey (1987)

Table 4. Indirect evidence of the efficacy of prophylaxis

	Amoxycillin-clavulanic acid (n = 138)	Metronidazole (n = 142)	P
Duration of postoperative hospital stay* (days) geometric mean	7·0	7·7	<0·01 (t = 2·8)
No (%) of patients remaining in hospital for >12 postoperative days†	5 (3·6)	9 (6·3)	0·5>P>0·2 (χ^2 = 1·1)
No (%) of patients requiring antibiotics for postoperative infection	18 (13·0)	41 (28·9)	<0·005 (χ^2 = 9·6)
No. (%) of patients requiring surgery for operative site infection	1 (0·7)	13 (9·2)	<0·005 (χ^2 = 8·8)

*Excluding the 44 cases of one consultant who had a policy of keeping patients in hospital for at least 12 postoperative days irrespective of clinical state. The t-test was performed on the logarithm of the number of days because the data followed a skewed distribution, d f = 235.

†Including the consultant's patients who are routinely kept in hospital for at least 12 postoperative days

issue. Clinical trials have almost consistently demonstrated a genuine benefit from prophylaxis in vaginal hysterectomy (Hirschmann & Inui 1980; Polk 1981). However, not all studies have reported a statistically significant reduction in postoperative infection in antibiotic recipients undergoing abdominal hysterectomy (Hirschmann & Inui 1980; Polk 1981). While this would suggest a larger protective effect from prophylaxis in vaginal than in abdominal hysterectomy, even this widely held view has been disputed when infection at the operative site only was considered (Shapiro *et al.* 1982). Hirschmann & Inui (1980), after reviewing the literature, concluded that the efficacy of prophylaxis is firmly established for vaginal hysterectomy but that the decision to use preventive antibiotics for abdominal hysterectomy should be left to the individual surgeon in the light of his previous experience of the prevalence of postoperative infection.

What remains to be established is the optimum regimen for those who choose to use prophylaxis in gynaecological surgery. Most operative site infections after hysterectomy are caused by a mixture of both aerobic and anaerobic organisms derived from the indigenous flora of the vagina and cervix (Allen *et al.* 1972; Ohm & Galask 1976). Anaerobes are the organisms numerically dominant at these sites and are also the pathogens most frequently isolated from posthysterectomy wound and vaginal vault infections (Study Group 1974). A number of studies have demonstrated the benefit of prophylaxis against anaerobes with metro-

Table 5. Pathogens recovered from postoperative infections

Site of infection	Amoxycillin-clavulanic acid No	Metronidazole No
Operative site		
Staphylococcus aureus	1	11
Group A beta haemolytic streptococcus	0	1
Group B beta haemolytic streptococcus	0	1
Bacteroides fragilis	0	1
Proteus sp.	0	2
No organism identified	2	2
Respiratory tract		
Haemophilus influenzae	0	5
Streptococcus pneumoniae	0	2
Urinary tract		
Escherichia coli	9	7
Streptococcus faecalis	0	7
Klebsiella sp	0	2
Proteus sp.	0	1
Other coliforms	0	1
Group B beta haemolytic streptococcus	0	1
Diphtheroids	0	1

nidazole (Study Group 1974; Appelbaum *et al.* 1978; Jackson *et al.* 1979; Hamod *et al.* 1980; Poulsen *et al.* 1984) and this agent, with or without an antimicrobial active against aerobes, is currently the regimen most popular with gynaecologists in the UK (Chapman & Rose 1986). However, although anaerobes are the major problem in gynaecological surgery, the cephalosporins, which are the agents most commonly used in North America (Hirschmann & Inui 1980; Polk 1981), have been highly successful in prophylaxis despite their limited activity against many anaerobes, particularly *B. fragilis.* It has been suggested that in dealing with a polymicrobial flora, prophylaxis need not be effective against all potential pathogens but that any antibiotic active against the aerobic or anaerobic flora would reduce postoperative sepsis (Polk *et al.* 1980; Hamod *et al.* 1982). While this is undoubtedly true, the present study has shown that a regimen which has activity against all potential pathogens is superior to one that is active only against anaerobes. Patients receiving amoxycillin-clavulanic acid had significantly less infectious morbidity and fewer operative site infections. They also remained in hospital for a significantly shorter period, required surgery for postoperative wound or pelvic infection less often, and received fewer therapeutic courses of antibiotics. Although we have not compared amoxycillin-clavulanic acid with an agent, such as a first generation cephalosporin, which has comparable activity against aerobic bacteria, we suspect that the former would provide superior prophylaxis, owing to its broader spectrum of activity against anaerobes. Support for this view can be found in the study of Hirsch *et al.* (1978) which reported that the use of two antibiotics (cephacetrile and ornidazole) to cover both aerobic and anaerobic organisms was more effective than either of the drugs alone.

The aerobic pathogen which has been isolated most frequently from operative site infections after gynaecological surgery is *E. coli* (Ledger *et al.* 1973; Ohm & Galask 1976, Stage *et al.* 1982) In the present study, however, in the group receiving metronidazole in which protection against aerobes was not provided, *S. aureus* was the most important aerobic organism isolated. As many strains of *E coli,* and most strains of *S. aureus,* are resistant to ampicillin, this agent would not be expected to provide adequate prophylaxis against these organisms. It would seem prudent, where activity against aerobes is desired, to include an agent with sufficient beta-lactamase stability to cover both *S aureus* and beta-lactamase-producing coliforms. As highly resistant organisms are rarely a problem in gynaecological surgery the use of very broad spectrum antibiotics is unnecessary. The requirements would adequately be met by either a first generation cephalosporin or amoxycillin-clavulanic acid.

Another aspect of prophylaxis which has not been precisely defined is the appropriate duration of antibiotic administration. In earlier studies antibiotics were prescribed for several days (Goosenberg *et al.* 1969; Allen *et al.* 1972, Ledger *et al.* 1973). Subsequently, three-dose regimens were shown to be as effective as prolonged courses (Ledger *et al* 1975; Glover & Nagell 1976) and were less likely to be associated with increased colonization of the vagina by resistant organisms (Ledger *et al.* 1975; Mendelson *et al.* 1979; Stage *et al.* 1982). More recently, a number of trials have demonstrated that a one-dose regimen is equivalent to three doses (Lett *et al.* 1977; Mendelson *et al.* 1979; Hamod *et al.* 1980). One study (Khan *et al.* 1981), however, reported that while two doses of metronidazole were superior to placebo, a single dose was not. Taken together these clinical trials confirm that a single pre-operative dose and perhaps one or two postoperative doses constitute adequate prophylaxis for hysterectomy. To prolong the duration would promote the emergence of resistant strains and increase both costs and risks of toxicity, without any demonstrable benefit to the patient.

In the present study bacteriuria was the most common reason for which antibiotics were prescribed in the postoperative period. While this observation has also been made by other investigators (Ledger *et al.* 1972; Mathews *et al.* 1977), there is considerable difference of opinion about the importance of urinary tract infection as a cause of morbidity after gynaecological surgery, or indeed, whether it can be prevented by prophylaxis (Ledger *et al.* 1975; Mendelson *et al.* 1979; Stage *et al.* 1982). Compared with metronidazole, which in this situation could be considered a placebo, amoxycillin-clavulanic acid did not significantly reduce the frequency of postoperative bacteriuria. But this agent did appear to influence the nature of the isolates. In the metronidazole group 7 of 20 isolates were faecal streptococci while in the amoxycillin-clavulanic acid group no faecal streptococci were isolated ($P<0{\cdot}05$). This cannot be explained simply by the fact that the streptococci would be sensitive to amoxycillin-clavulanic acid because 7 of the 9 strains of *E. coli* isolated from the urine of patients in group 1 were also sensitive to amoxycillin-clavulanic acid. Additional trials which should involve large numbers of patients will be necessary to clarify the role of perioperative antibiotics in this context

The results of this study suggest that the ideal prophylactic regimen for hysterectomy should consist of an agent, or combination of agents, with activity against both aerobic and anaerobic potential pathogens. Whether one uses a combination, such as a first generation cephalosporin plus metronidazole, or amoxycillin-clavulanic acid, which would probably be equally as effective but with the obvious advantage of administering a single agent, will largely be influenced by cost and convenience.

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References

Allen, J. L., Rampone, J F & Wheeless, C. R. (1972) Use of a prophylactic antibiotic in elective major gynaecologic operations *Obstet Gynecol* **39**, 218-224.

Appelbaum, P. C , Moodley, J , Chatterton, S A., Cowan, D. B. & Africa, C W. (1978) Metronidazole in the prophylaxis and treatment of anaerobic infection. *S Afr Med J* **54**, 703-706.

Blackmore, M. A., Turner, G M., Adams, M R. & Speller, D C. E (1981) The effect of preoperative povidone iodine vaginal pessaries on vault infections after hysterectomy *Br J Obstet Gynaecol* **88**, 308-313

Brown, E. M (1984) The in-vitro susceptibility of the *Bacteroides fragilis* group to amoxycillin-clavulanic acid *J Antimicrob Chemother* **14**, 367-372.

Chapman, M G. & Rose, G. L. (1986) Prophylactic antibiotics in gynaecological surgery Abstracts of the twenty-fourth British Congress of Obstetrics and Gynaecology, 41

Goosenberg, J., Emich, J P & Schwarz, R. H. (1969) Prophylactic antibiotics in vaginal hysterectomy *Am J Obstet Gynecol* **105**, 503-506

Glover, M W & Nagell, J R Jr (1976) The effect of prophylactic ampicillin on pelvic infection following vaginal hysterectomy. *Am J Obstet Gynecol* **126**, 385-388.

Hamod, K A., Spence, M. R & King, T M. (1982) Prophylactic antibiotics in vaginal hysterectomy a review *Obstet Gynecol Surv* **37**, 207-216.

Hamod, K. A , Spence, M R , Rosenshein, N B & Dillon, M. B (1980) Single and multidose prophylaxis in vaginal hysterectomy· a comparison of sodium cephalothin and metronidazole. *Am J Obstet Gynecol* **136,** 976-979

Hirsch, H. A , Decker, K & Kadauke, A (1978) Perioperative prophylaxis with cephacetrile and ornidazole in hysterectomies. 18th Interscience Conference on Antimicrobial Agents and Chemotherapy, Atlanta, GA

Hirschmann, J V. & Inui, T S (1980) Antimicrobial prophylaxis. a critique of recent trials *Rev Infect Dis* **2,** 1-23.

Jackson, P., Ridley, W. J & Pattison, N S (1979) Single dose of metronidazole prophylaxis in gynaecological surgery *NZ Med J* **89,** 243-247.

Khan, M , Begg, H. B , Frampton, J. & Hughes, T. B (1981) A comparative study of the prophylactic effect of one dose and two dose intravenous metronidazole therapy in gynaecological surgery *Scand J Infect Dis* **26 (Suppl.),** 115-117.

Ledger, W. J., Gee, C. & Lewis, W. P. (1975) Guidelines for antibiotic prophylaxis in gynaecology *Am J Obstet Gynecol* **121,** 1038-1045

Ledger, W. J., Rete, A & Headington, J. T. (1972) The surveillance of infection of an inpatient gynecology service. *Am J Obstet Gynecol* **113,** 662-666.

Ledger, W J , Sweet, R. L. & Headington, J. T. (1973) Prophylactic cephalоridine in the prevention of postoperative pelvic infections in premenopausal women undergoing vaginal hysterectomy *Am J Obstet Gynecol* **115,** 766-774.

Lett, W. J., Ansbacher, R., Davison, B. L. & Otterson, W. N. (1977) Prophylactic antibiotics for women undergoing vaginal hysterectomy *J Reprod Med* **19,** 51-54.

Mathews, D D., Ross, H & Cooper, J (1977) A double-blind trial of single-dose chemoprophylaxis with cotrimoxazole during total abdominal hysterectomy. *Br J Obstet Gynaecol* **84,** 894-897.

Mendelson, J., Portnoy, J , De Saint Victor, J. R. & Gelford, M. (1979) Effect of single and multidose cephradine prophylaxis on infectious morbidity of vaginal hysterectomy. *Obstet Gynecol* **53,** 31-35.

Neu, H. C & Fu, K. P. (1978) Clavulanic acid, a novel inhibitor of beta-lactamases *Antimicrob Agents Chemother* **14,** 650-655.

Ohm, M. J & Galask, R. P (1976) The effect of antibiotic prophylaxis on patients undergoing total abdominal hysterectomy I Effect on morbidity. *Am J Obstet Gynecol* **125,** 442-447.

Polk, B F. (1981) Antimicrobial prophylaxis to prevent mixed bacterial infection. *J Antimicrob Chemother* **8 (Suppl. D),** 115-129.

Polk, B F., Tager, I B., Shapiro, M , Goren-White, B., Goldstein, P & Schoenbaum, S. C (1980) Randomised clinical trial of perioperative cefazolin in preventing infection after hysterectomy *Lancet* **i,** 437-441

Poulsen, H K , Borel, J. & Olsen, H (1984) Prophylactic metronidazole or suction drainage in abdominal hysterectomy. *Obstet Gynecol* **63,** 291-294

Shapiro, M., Munoz, A., Tager, I B., Schoenbaum, S.C & Polk, B. F. (1982) Risk factors for infection at the operative site after abdominal or vaginal hysterectomy *N Engl J Med* **307,** 1661-1666

Stage, A H., Glover, D D. & Vaughan, J. E. (1982) Low-dose cephradine prophylaxis in obstetric and gynecologic surgery. *J Reprod Med* **27,** 113-119.

Study Group (1974) Metronidazole in the prevention and treatment of bacteroides infections in gynaecological patients. *Lancet* **ii,** 1540-1543.

Wise, R., Andrews, J. M. & Bedford, K. A. (1978) In-vitro study of clavulanic acid in combination with penicillin, amoxycillin and carbenicillin *Antimicrob Agents Chemother* **13,** 389-393.

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Concomitant zoonotic infections with ovine *Chlamydia* and 'Q' fever in pregnancy: clinical features, diagnosis, management and public health implications.

Case report

D. McGIVERN, R. WHITE, I. D. PAUL, E. O. CAUL,
A. P. C. H. ROOME, D. WESTMORELAND

Case report

A 30-year-old pregnant woman, the wife of a sheep farmer in the Cotswolds, was admitted to hospital on 28 March 1986 with fever, breathlessness and jaundice. She first became unwell about 6 weeks earlier, at 8 weeks gestation, with fever, sore throat and generalized arthralgia. These symptoms settled spontaneously after 2 weeks. Two weeks later she became ill again with fever, arthralgia, cough and retrosternal pain. On this occasion she was treated with oral erythromycin 500 mg, four times daily, for 7 days. At the end of the treatment she was no better and 3 days later became jaundiced and was admitted to hospital. On the day before admission her haemoglobin was 11·0 g/dl, white cell count 4·8 × 10^{12} cells/l (69% neutrophils, 30% lymphocytes), platelet count was reduced at 34 × 10^{12}/l. Liver function tests were abnormal: bilirubin 95 μmol/l (normal range 5–17 μmol/l), alanine amino transaminase 48 i u./l (normal <40 i.u /l), alkaline phosphatase 930 i u./l (normal range 8–120 i.u./l), albumin 22 g/l (normal range 35–40 g/l).

On admission she was thin, unwell, and jaundiced with a temperature of 38·5 °C and a respiratory rate of 28/min. A soft and tender liver was palpable and there was a tender 2 cm spleen The uterine size was compatible with a 15-week pregnancy. A chest radiograph showed patches of consolidation in the right lower and middle lobes. Ultrasound scan of the liver was normal but pelvic ultrasound revealed an immobile non-viable fetus. Blood gases confirmed hypoxia with respiratory alkalosis. Her haemoglobin was 11·4 g/dl, white blood count 7·4 × 10^9/l (81% neutrophils); the platelet count had returned to normal at 184 × 10^9/l; urea and electrolytes were normal. Liver function tests were bilirubin 39 μmol/l, alanine aminotransferase 32 i.u./l, alkaline phosphatase 1233 i.u./l. The infective agents which were considered as a cause for her pneumonia and jaundice included *Coxiella burnetii, Mycoplasma pneumoniae, Chlamydia psittaci, Legionella pneumophila,* influenza 'A' and 'B', *Leptospira* and cytomegalovirus. Hepatitis A and B were also considered in view of the jaundice. Treatment was commenced with intravenous erythromycin 500 mg four times daily, together with ampicillin 500 mg four times daily. The fever settled within 48 h of admission and at this time a dead fetus was aborted spontaneously

Department of Medicine, Frenchay Hospital, Bristol
D McGIVERN *Senior Medical Registrar*
R WHITE *Consultant Physician*

Joint Regional Public Health and District Virus Laboratory, Bristol
I D PAUL *Senior MLSO*
E O CAUL *Top Grade Microbiologist*
A. P C H. ROOME *Consultant Virologist*
D. WESTMORELAND *Assistant Microbiologist*

Correspondence: D. McGivern

Serological investigations

An antenatal serum sample collected 7 days after the patient's first illness was available for comparison with a serum sample collected 5 weeks later, namely 2 weeks after the beginning of the second illness. These serum samples were examined by the complement fixation test (CFT) for evidence of influenza A and B, *C. burnetii* (phase 2), *M. pneumoniae,* cytomegalovirus, leptospirosis, and psittacosis infections. Sera were also examined for *L. pneumophila* antibodies using the indirect immunofluorescence technique (IF). These results are shown in Table 1. In addition all markers for hepatitis A and B were negative.

The IF technique was used to identify IgM antibody to *C. burnetii* using yolk-sac propagated *C. burnetii*. *C. psittaci* antibodies (IgG and IgM) were detected by IF staining of whole inclusion bodies in McCoy cells (Richmond & Caul 1975), infected with *C. psittaci* (ovine strain EAE) and *Chlamydia trachomatis* (LGV serotype 2). Comparable IgG IF titres were obtained with both *Chlamydia* antigens (Table 1).

Examination of fetal tissue for C. psittaci *and* C. burnetii *antigen*

Impression smears were prepared from fetal heart, lung, brain, liver and placenta and fixed in acetone at room temperature for 10 min. All smears were stained with a genus-specific FITC labelled *Chlamydia* monoclonal antibody (IMAGEN, Boots Celltech) and with a *C. trachomatis* species-specific FITC labelled monoclonal antibody (MICROTRAK, Syva Laboratories). *Chlamydia* antigen could only be detected in smears prepared from the placenta and this antigen was only reactive with the genus-specific monoclonal antibody. The positive results obtained with the genus-specific antibody demonstrated that the antigen detected was *C. psittaci* and not *C. trachomatis*. The pattern of stainable antigen detected by the genus-specific antibody was of particular interest. Many cells contained large amounts of antigen of similar appearance to the intracytoplasmic inclusions detected in primary EAE infected cell cultures. In addition large amounts of extracellular antigen (elementary bodies and lipopolysacharide antigen) were seen which were indistinguishable from those previously described in clinical specimens containing *C. trachomatis* (Alexander *et al.* 1985). Duplicate smears of fetal tissues were also examined by indirect immunofluorescence for *C. burnetii* antigen. All smears were negative.

Table 1. Results of complement fixation tests on paired sera

	Serum of 20.2.86 (titre)	Serum of 27.3.86 (titre)
Influenza A	<8	192
Influenza B	<8	<8
Chlamydia psittaci	<8 (IF titre <16)†	768* (IF titre 1024)†
Coxiella burnetii	48‡	1024
Legionella pneumophila	<8	<8
Mycoplasma pneumoniae	<8	<8

C. psittaci-specific IgM-positive (by immunofluorescence).

†Immunofluorescence using ovine strain of *C. psittaci* and L2 strain of *C. trachomatis* (the comparable titres obtained with these two antigens indicates a genus-specific response, i.e group)

‡*C burnetii*-specific IgM-positive (by immunofluorescence)

Isolation of C. psittaci *and* C. burnetii

The placenta and fetal organs were homogenized and inoculated into McCoy cell cultures as described previously (Richmond *et al.* 1980). After 3 and 5 days incubation, monolayers were fixed and stained with both genus- and species-specific FITC labelled monoclonal antibodies and examined by incident blue-light microscopy. Intracytoplasmic inclusions were only demonstrated using the genus-specific monoclonal antibody, confirming this was a *C. psittaci* strain (Fig. 1). The isolate was then passaged until a high multiplicity of infection was obtained in cell culture (90–100% of the cells infected). It was further passaged at the Moredun Institute, Edinburgh, before DNA analysis of the isolate was carried out by restriction endonuclease (McClenaghan *et al.* 1984). The results of this analysis conclusively demonstrated that this *C. psittaci* strain was of ovine origin.

No evidence of placental or fetal infection with *C. burnetii* could be demonstrated after intraperitoneal inoculation of guinea-pigs.

Treatment and outcome

When the results of the serology were known (after the fetus had aborted) erythromycin and ampicillin were stopped and doxycycline 100 mg per day was substituted and continued for 10 days. Three days after admission to hospital the jaundice and fever had settled. She was discharged 4 days later. When reviewed in an outpatients clinic 2 weeks later, the chest

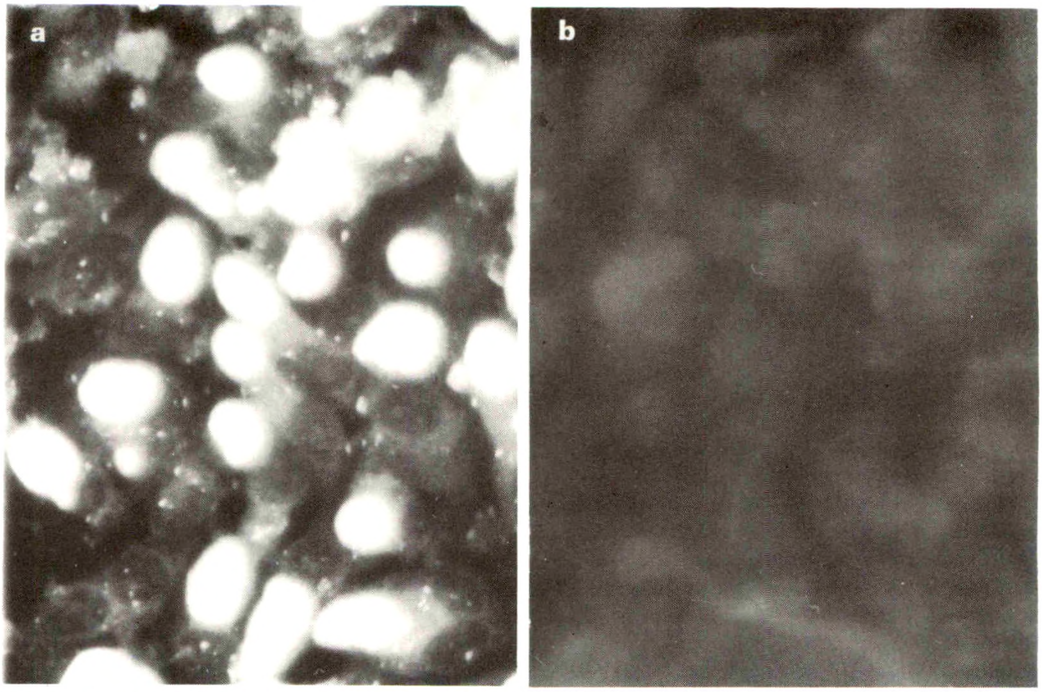

Fig. 1. (a) Intracytoplasmic inclusion bodies of *Chlamydia psittaci* stained with genus-specific monoclonal antibody; (b) same preparation stained with species-specific monoclonal antibody.

radiograph, blood count and liver function tests were normal.

Discussion

The agent causing enzootic abortion in ewes (EAE) was first described by Stamp *et al.* (1950). Sheep acquire the infection by contact with placentas of aborted lambs and uterine discharges heavily contaminated with *C. psittaci*. Since the mid 1950s vaccines against EAE have been available in the UK (McEwan & Foggie 1956), but protection has never been total and the disease has persisted. There is evidence that the disease prevalence has increased in recent years (Linklar & Dyson 1979).

Since 1967 there have been six documented cases of chlamydial infection in women during the second and third trimester of pregnancy (Roberts *et al.* 1967; Beer *et al.* 1982; Johnson *et al.* 1982; McKinley *et al.* 1985). In five cases there was direct contact with ewes during the lambing season. Miscarriage occurred in five patients and all the women were acutely ill, most with disseminated intravascular coagulation, renal failure or jaundice. The correct diagnosis was not made promptly in any patient and one fatality has occurred. In most patients retrospective diagnoses were made by complement fixation tests which do not distinguish between disseminated *C. psittaci* and *C. trachomatis* infection. In one patient, however, *Chlamydia* antigens were identified in fetal lung, liver and placenta, and although the organism was isolated from fetal heart and placenta it was not specifically identified as EAE (Johnson *et al.* 1982).

The husband of the patient described in our studies owned a flock of British Friesland milking sheep which had experienced an abortion problem in January 1985. Enzootic abortion was diagnosed following the demonstration of *C. psitaci* inclusion bodies in modified Ziehl-Nielsen smears from thickened placenta, and high CF titres to *C. psittaci* in the blood of aborting ewes. After this outbreak the flock was vaccinated in the autumn of 1985 and there were no further abortions during the lambing season of 1986. After the patient's illness blood samples from 13 ewes in the flock all had demonstrable antibody to *C. psittaci* and *C. burnetii* (CFT).

In contrast to previous reports, EAE infection in our patient occurred in the first trimester of pregnancy. The patient presented with a biphasic illness which began 6 weeks before admission. The first illness can be attributed to

'Q' fever infection since a low level of *C. burnetii* CF antibody (phase 2) was present in the serum sample taken at that time which was also IgM positive. The antibody titre subsequently rose to a high level (Table 1). Positive CFT in the 13 ewes tested suggested that the sheep were the likely source of 'Q' fever infection and zoonotic infections following contact with pregnant sheep are well recognized (Hall *et al* 1982; Stoker & Marrion 1955). After resolution of the first illness, without treatment, she became unwell 2 weeks later. On this occasion serological evidence suggested infection with influenza A, which was circulating in the community at the time, and *C. psittaci*. The rise in antibody to influenza A and *C. burnetii* did not represent an anamnestic response since other antibodies tested in parallel (influenza B, *L. pneumophila* and *M. pneumoniae*) were negative. It is likely that the onset of jaundice and transient thrombocytopenia, suggesting disseminated intravascular coagulation, was related to infection with *C. psittaci*. The patient's pneumonia may have been caused by EAE, but equally could be ascribed to any of the three infecting agents documented. The isolation of *C. psittaci* from placenta confirmed this to be the cause of the spontaneous abortion and subsequent DNA analysis has demonstrated that the isolate is of ovine origin (McClenaghan *et al.* 1984; A. Herring, N. Inglis & I. Anderson, personal communication). The use of genus-specific and species-specific monoclonal antibodies enabled rapid identification of *C. psittaci* from placental tissue.

This is the first case in which pneumonia has been documented in association with proven EAE infection. However, Dale (1983) reported an influenza-type illness with cough in three shepherds, a shepherd's wife and a conservation officer who were exposed to aborting ewes (Dale 1983). In these cases infection with *C. psittaci* was suspected from the presence of high CF antibody titres in serum samples collected at the time of examination. It is likely therefore that ovine *C. psittaci* is a cause of upper respiratory tract symptoms in humans and may be a previously unrecognized cause of pneumonia. Our patient's husband had serological evidence of previous chlamydial infection but he was only able to recall coughs and colds in the previous 12 months.

This report adds to the accumulating evidence that *C. psittaci* of ovine origin is a hazard to pregnant women in the farming community. A worrying feature in our patient was the exact mode of transmission. The patient was aware of possible infection and specifically avoided contact with sheep or sheep's milk from the onset of her pregnancy. Transmission from contaminated fomites, on working clothes, or via airborne routes, as postulated for 'Q' fever infection, must be considered. It is particularly disturbing that in this and two previous cases (Roberts *et al.* 1967; McKinley *et al.* 1985), there was no history of direct contact with aborted ovine products. The public health implications in the farming community are therefore considerable. Five of the six patients with possible or proven miscarriage due to EAE have been reported during the last 4 years, a period when control of the disease in lambing flocks has deteriorated.

The pregnant woman described in this report became infected with ovine *C. psittaci* despite vaccination of the flock and an absence of abortions in ewes. This suggests that subclinical chlamydial infection in sheep constitutes a risk to human pregnancy. General practitioners and veterinarians serving the farming community should now be made aware of this problem. During the lambing season serious consideration should be given to the use of erythromycin for the treatment of pyrexia of unknown origin in pregnant women from rural areas. However, it remains to be seen whether early treatment can prevent chlamydia-associated abortions in women. Prospective studies are now required to determine the magnitude of the problem in the farming community as well as in rural areas where sheep farming occurs.

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References

Alexander, I., Paul, I. D. & Caul, E. O (1985) Evaluation of a genus reactive monoclonal antibody in rapid identification of *Chlamydia trachomatis* by direct immunofluorescence *Genitourin Med* **61,** 245-254

Beer, R. J S , Bradford, W. P & Hart, R J C (1982) Pregnancy complicated by psittacosis acquired from sheep *Br Med J* **284,** 1156-1157.

Dale, B (1983) Psittacosis of suspected ovine origin *Communicable Dis (Scotland)* **83/326,** viii

Hall, C J , Richmond, S J., Caul, E O., Pearce, N H. & Silver, I. A. (1982) Laboratory cutbreak of 'Q' fever acquired from sheep. *Lancet* **l,** 1004-1006

Johnson, F W A , Matheson, B A., Williams, H. *et al* (1982) Abortion due to infection with *Chlamydia psittaci* in a sheep farmer's wife *Br Med J* **290,** 592-594

Linklar, K A. & Dyson, D A (1979) Field studies on enzootic abortion of ewes in South East Scotland *Vet Rec* **105,** 387-389

McClenaghan, M , Herring, A H & Aitken, J D (1984) Comparison of *Chlamydia psittaci* isolates by DNA restriction endonuclease analysis. *Infect Immun* **452,** 384-389

McEwan, A D & Foggie, A (1956) Enzootic abortion in ewes Prolonged immunity following the injection of adjuvant vaccine *Vet Rec* **68,** 686-689

McKinley, A W., White, N , Buxton, D., Inglis, J. M., Johnson, F. W. A., Kurtz, J B & Bahle, B. P. (1985) Severe *Chlamydia psittaci* sepsis in pregnancy. *Q J Med* **57,** 689-696.

Richmond, S J & Caul, E O. (1975) Fluorescent antibody studies in chlamydial infections *J Clin Microbiol* **1,** 345-352

Richmond, S J , Paul, I D & Taylor, P K (1980) Value and feasibility of screening women attending STD clinics for cervical chlamydial infections. *Br J Vener Dis* **56,** 92-95

Roberts, W , Grist, N R & Giroud, P (1967) Human abortion associated with ovine abortion agent *Br Med J* **4,** 37

Stamp, J T , McEwan, A D , Watt, J A A & Nisbet, D. I (1950) Enzootic abortion in ewes. Transmission of the disease. *Vet Rec* **62,** 251-254

Stoker, M G P & Marrion, B P (1955) The spread of 'Q' fever from animals to man. The natural history of rickettsial disease *Bull WHO* **13,** 781-806

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Recurrent intracranial haemorrhages *in utero* in an infant with alloimmune thrombocytopenia. Case report

L. S. DE VRIES, J. CONNELL, G. M. BYDDER, L. M. S. DUBOWITZ, C. H. RODECK, R. S. MIBASHAN, A. H. WATERS

Case report

The male infant described in this report was the second child of healthy parents. The first child was born by an uncomplicated vaginal delivery at term. Petechiae were noted shortly after birth and the infant's platelet count was found to be only 9×10^9/l. The haemoglobin was 15·5 g/dl and a clotting screen was normal. The haemoglobin fell to 10·6 on day 5 and transfusions of fresh blood and random donor platelets were given. No particular rise of the platelet count was noted after the transfusion. On day 11, a CT scan showed a partly organized intracranial haemorrhage. The megakaryocytes were normal in the bone marrow and platelet serology demonstrated a strong reaction between the mother's serum and the father's platelets which was subsequently shown to be due to anti-Pl A1. The diagnosis of alloimmune thrombocytopenia was made and treatment with corticosteroids was started. This did not result in a rapid rise of the platelets, which were still only 46×10^9/l at 6 weeks of age and 97×10^9/l at 9 weeks of age. The child required insertion of a ventriculo-peritoneal shunt and subsequently developed hemiplegia and visual impairment.

Platelet typing of the parents showed the mother to be Pl A1 negative and the father homozygous Pl A1 positive. HLA typing showed that the mother had the HLA-B8 antigen, which is closely associated with the ability of Pl A1 negative individuals to make anti-Pl A1 on exposure to the Pl A1 antigen (Reznikoff-Etievant *et al.* 1981). When the mother became pregnant again, close obstetrical supervision was started at 7 weeks gestation. Ultrasound scans of the fetal head performed at 10, 22, 28 and 32 weeks gestation were all normal. Maternal Pl A1 antibody titre rose from 1:16 to 1:64 at 22 weeks gestation and she was admitted at 35 weeks gestation for further ultrasound studies and fetal blood sampling. On admission the cardiotocogram (CTG) was noted to be unreactive and ultrasonography of the fetal head showed dilated ventricles with a left parenchymal haematoma anteriorly (Fig. 1). Ultrasound-guided needle puncture of the umbilical vein was performed (Nicolaides *et al.* 1986). The initial fetal blood sample was severely thrombocytopenic (12×10^9/l) and 35 ml of platelets concentrate (prepared by plateletpheresis of a selected group O Pl A1 negative donor) were infused into the umbilical circulation; the post-transfusion platelet count was 139×10^9/l. After the transfusion the baby was born by an uneventful caesarean section at 35 weeks. Subsequent changes in the infant's platelet count are shown in Fig. 2. The infant was in good condition at birth with Apgar scores of 7 and 10 at 1 and 5 min respectively. The birthweight was 2430 g (25th centile) and head circumference 35 cm (>90th centile). The infant's condition remained stable until 18 h of age, when a generalized convulsion occurred, which was treated with a loading dose

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Hammersmith Hospital, London W12
Department of Paediatrics and Neonatal Medicine
L. S. DE VRIES
J. CONNELL
L M. S. DUBOWITZ

Department of Diagnostic Radiology (MRI Unit)
G. M. BYDDER

Institute of Obstetrics and Gynaecology, Queen Charlotte's Maternity Hospital, London W6
C. H. RODECK

Department of Haematology, King's College Hospital, Denmark Hill, London SE5
R S. MIBASHAN

Department of Haematology, St Bartholomew's Hospital and Medical College, London EC1
A. H. WATERS

Correspondence Dr L. M S. Dubowitz, Hammersmith Hospital, Department of Paediatrics, Du Cane Road, London W12 0HS

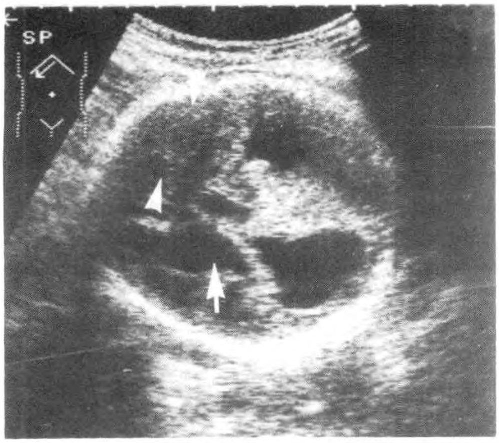

Fig. 1. Antenatal ultrasound scan of the fetal head, showing dilated ventricles (arrow) and a left anterior parenchymal haematoma (arrowhead).

of phenobarbitone (20 mg/kg). The baby was then referred to the Hammersmith Hospital for further neurological investigations.

On clinical examination the infant showed slight asymmetry in tone, general hypotonia and poor visual orientation. A 24-h continuous four-channel EEG recording showed a few short seizures and a strikingly abnormal pattern with a discontinuous pattern on a very low background amplitude. An ultrasound scan showed ventricular dilatation, a partly echolucent, partly echodense area in the left parieto-temporal parenchyma and an echolucent area in the right parieto-temporal region (Fig. 3a). Cystic changes, compatible with extensive cystic leukomalacia were also noted, mainly around the right lateral ventricle (Fig. 3b). A CT scan showed evidence of a subarachnoid haemorrhage, an area in the left parieto-temporal region suggestive of a haematoma and two further porencephalic cysts suggestive of older haematomas. No cysts were seen in the periventricular region, but areas of decreased attenuation were present. Magnetic resonance imaging was performed, using a low field magnet (0·15 Tesla). Both the inversion recovery sequence and a special sequence used to identify susceptibility changes were consistent with an old haemorrhage (>4 weeks) in the right hemisphere and two more recent ones in the left hemisphere (1–4 weeks) (Sipponen *et al.* 1983; Gomori *et al.* 1985) (Fig. 4a). Evidence of a subarachnoid haemorrhage was also noted (Fig. 4b).

Discussion

This case has demonstrated that infants at risk of neonatal alloimmune thrombocytopenia (NAT) can develop intracranial haemorrhages during the third trimester of pregnancy and on more than one occasion. This emphasizes that the management of infants at risk of alloimmune thrombocytopenia is more complicated than has previously been appreciated.

Intracranial haemorrhage is the most serious complication of NAT and leads to death or later neurological disabilities in about 15% (Pearson *et al.* 1964; Muller *et al.* 1985). As it has been assumed that the birth process is the main risk factor for central nervous system bleeding, Sitarz *et al.* (1976) advised delivery of infants at risk of alloimmune thrombocytopenia by elective caesarean section in order to avoid central nervous system haemorrhages. An increasing number of cases of NAT have been reported since then where there was evidence of an intracranial haemorrhage occurring before delivery (Zalneraitis *et al.* 1979; Sia *et al.* 1985; Lam & Shulman 1985; Friedman & Aster 1985; Morales & Stroup 1985). Therefore, attempts have been made to identify the severely affected infants during pregnancy. As routine antenatal screening does not include Pl A1 typing of the mother, the first affected infant is usually unexpected and diagnosis is made after delivery. In assessing the

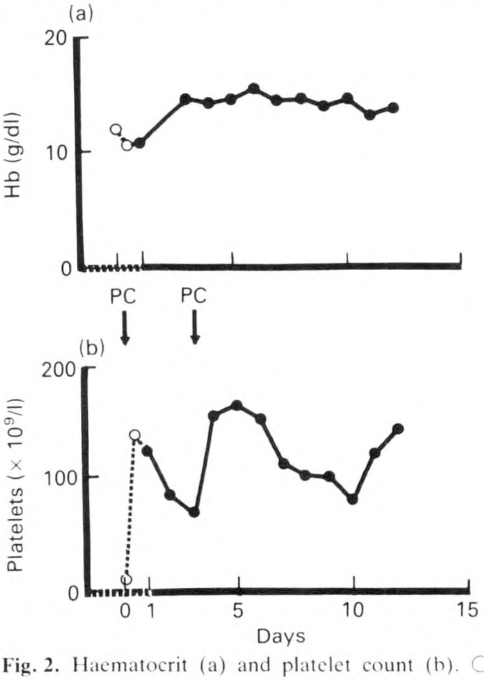

Fig. 2. Haematocrit (a) and platelet count (b). ○, Values for the intrauterine samples before and after platelet transfusion, cord blood values are indicated on day 1; ●, postnatal values. PC, Pl A1 negative platelet concentrate transfusion.

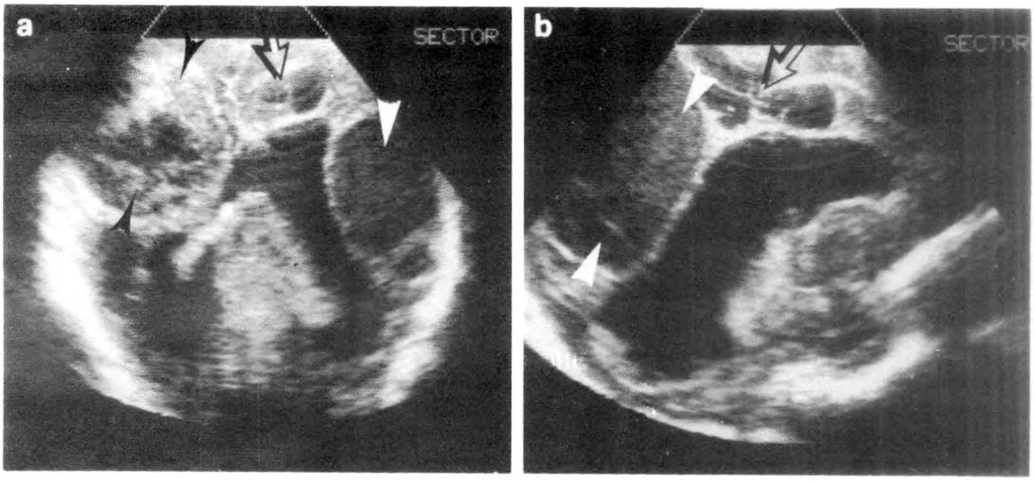

Fig. 3. (a) Cranial ultrasound, coronal view angling the scanhead backwards, showing dilated ventricles, a large echolucent area (arrowhead) in the right hemisphere and a partly echodense area in the left hemisphere (black arrowheads). Small periventricular cystic lesions are noted around the ventricle (open arrow). (b) A right parasagittal view showing the large echolucent area behind the occipital horn of the lateral ventricle (arrowhead) and multiple periventricular cysts in the fronto-parietal region (open arrow).

risk of subsequent pregnancies being affected, it is helpful to determine the Pl A1/Pl A2 genotype of the father. The predictive value of the platelet antibody titre is limited and although a rising titre will usually indicate that the infant is Pl A1 positive, severely affected infants have been born to mothers with low antibody titres (Shulman *et al.* 1964).

Invasive antenatal diagnosis and treatment was described by Daffos *et al.* (1984). They per-

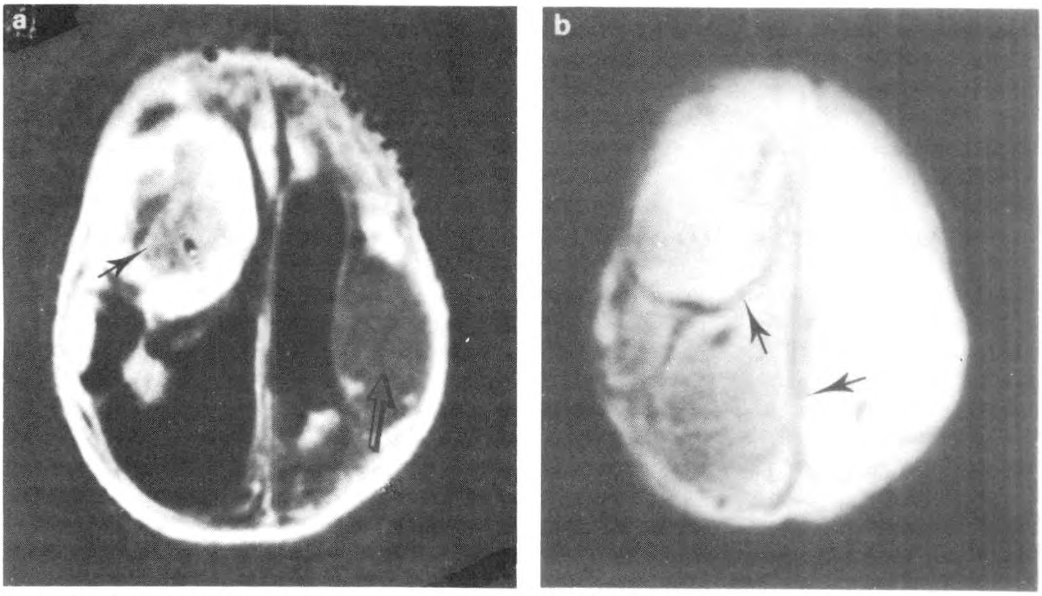

Fig. 4. MRI studies: (a) Inversion recovery sequence (IR 1800/600/33) showing subacute haematoma (dark arrows) and chronic haematoma (open arrow). (b) Dark regions are seen at the margins of the haematomas and ventricles on the corresponding partial saturation (PS 1660/193) image (arrows). The dark areas are probably due to haemoglobin degradation products.

formed fetal blood sampling at 32 weeks gestation and found severe thrombocytopenia. An intravascular transfusion with Pl A1 negative platelets was given at 37 weeks gestation just before delivery by caesarean section. The infant did not develop any problems after birth, but in comparison with our case, the fetus was still at risk of bleeding between 32 and 37 weeks.

Repeated fetal blood sampling and repeated intravascular platelet transfusions were suggested by Daffos *et al.* (1984) but effective management appears to be difficult, as the life span of the transfused platelets is only 8–10 days.

It is of interest that more than one infant with an intracranial haemorrhage due to NAT is often recorded in one family (Sia *et al.* 1985; Lam & Shulman 1985; Friedman & Aster 1985). As only 10–15% of the infants with NAT are reported to develop central nervous system lesions, this suggests that certain families are particularly at risk for these severe complications. Apart from a previously affected infant, there is no other indicator of these high-risk families at present.

This case illustrates that one should not underestimate the risk of a second child in a family being severely affected even when very careful monitoring and obstetrical management is provided.

Early fetal blood sampling, followed by repeated platelet transfusions with or without early delivery may be the only way to prevent the occurrence of intracranial haemorrhages in infants with alloimmune thrombocytopenia.

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References

Daffos, F., Forestier, F., Muller, J. Y., Reznikoff-Etievant, M. F., Habibi, B., Capella-Pavloska, M., Maigret, P. & Kaplan, C. (1984) Prenatal treatment of alloimmune thrombocytopenia. *Lancet* **ii,** 632.

Friedman, J. M. & Aster, R. H. (1985) Neonatal alloimmune thrombocytopenic purpura and congenital porencephaly in two siblings, associated with a 'new' maternal antiplatelet antibody. *Blood* **65,** 1412-1415.

Gomori, J. M., Grossmann, R. I., Goldberg, H. I., Zimmerman, R. A. & Bilaniuk, L. T. (1985) Intracranial haematomas: imaging by high-field MR. *Radiology* **157,** 87-93.

Lam, A. H. & Shulman, L. A. (1985) Ultrasound in congenital intracranial haemorrhage secondary to isoimmune thrombocytopenia. *Pediatr Radiol* **15,** 8-11.

Morales, W. J. & Stroup, M. (1985) Intracranial haemorrhage *in utero* due to isoimmune neonatal thrombocytopenia. *Obstet Gynecol* **65,** 20S-21S.

Muller, J. Y., Reznikoff-Etievant, M. F., Patereau, C., Dangu, C. & Chesnell, N. (1985) Thrombopénies néo-natales allo-immunes. Etude clinique et biologique de 84 cas. *Presse Med* **14,** 83-86.

Nicolaides, K. H., Soothill, P. W., Rodeck, C. H. & Campbell, S. (1986) Ultrasound-guided sampling of umbilical cord and placental blood to assess fetal wellbeing. *Lancet* **i,** 1065-1067.

Pearson, H. A., Shulman, N. R., Marder, V. J. & Cone, T. E. (1964) Isoimmune neonatal thrombocytopenic purpura. Clinical and therapeutic considerations. *Blood* **23,** 154-176.

Reznikoff-Etievant, M. F., Dangu, C. & Lobet, R. (1981) HLA-B8 antigen and anti-PL A1 alloimmunisation. *Tissue Antigens* **18,** 66-68.

Shulman, N. R., Marder, V. J. & Hillar, M. C. (1964) Platelet and leucocyte antigens and their antibodies. Serologic physiologic and clinical studies. *Prog Hematol* **4,** 222-296.

Sia, C. G., Amigo, N. C., Harper, R. G., Farahani, G. & Kochen, J. (1985) Failure of caesarean section to prevent intracranial haemorrhage in siblings with isoimmune thrombocytopenia. *Am J Obstet Gynecol* **135,** 79-81.

Sipponen, J. T., Sepponen, R. E. & Sivula, A. (1983) Nuclear magnetic resonance (NMR) imaging of intracranial haemorrhage in the acute and resolving phases. *J Comput Assist Tomogr* **7,** 954-959.

Sitarz, A. L., Driscoll, J. M. & Wolff, J. A. (1976) Management of isoimmune neonatal thrombocytopenia. *Am J Obstet Gynecol* **124,** 39-42.

Zalneraitis, E. L., Young, R. S. K. & Krisnamoorthy, K. S. (1979) Intracranial haemorrhage *in utero* as a complication of isoimmune thrombocytopenia. *J Pediatr* **95,** 611-614.

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Prolonged maternal indomethacin therapy associated with oligohydramnios. Case reports

W. DE WIT, I. VAN MOURIK, P. F. WIESENHAAN

Case report

Patient 1

A 35-year-old patient was admitted to the antenatal ward of our hospital in the 24th week of her first pregnancy with preterm contractions.

She had conceived after 7 years of primary infertility and had a uterus bicornis with a rudimentary horn. Except for the discovery of a myoma (diameter 7 cm on ultrasonography) in the anterior wall of the uterus, close to the internal os, and the development of anaemia (Hb 9·8 g/dl), which was treated wtih ferrofumarate and folic acid, pregnancy had been uneventful until admission.

As previous chromosome analysis and ultrasonographic screening of the fetus had revealed no congenital abnormalities, it was decided to start intravenous tocolytic therapy with fenoterol (Partusisten). However, up to 0·008 mg/min of fenoterol did not arrest the preterm contractions, so that treatment was extended by adding indomethacin (Indocid), administered as suppositories in a dose of 3 × 25 mg per day and hydroxyprogesterone (Proluton depot) 500 mg twice weekly intramuscularly. This combination finally arrested the preterm contractions. Treatment with hydroxyprogesterone, indomethacin and fenoterol was maintained until 31, 32 and 35 weeks gestation, respectively.

Three and a half weeks after the initiation of treatment with indomethacin a reduction was noted in the amount of amniotic fluid, which had been normal until then. During further indomethacin treatment the depth of the largest pool of amniotic fluid (measured as described by Chamberlain *et al.* 1984) remained between 1·7 and 2·2 cm, but filling of the fetal bladder could be seen on several occasions. Within a week after stopping indomethacin treatment the amount of amniotic fluid increased (depth of the largest pool of amniotic fluid 4·4 cm).

Except for a transient, slight rise of the transaminases (ALT 133 U/l; AST 86 U/l; LDH and γ-GT remained within normal limits) after initiation of tocolytic therapy, all other fetal and maternal measurements were within normal limits until 35 weeks, when the patient noted the absence of fetal movements. Since no fetal movements were seen by ultrasonography and urinary oestriol excretion decreased and because of the position of the large uterine myoma, a normal vaginal delivery did not seem possible, she was delivered by caesarean section.

The female infant weighed 3175 g and did not have any congenital abnormality. She did well after birth and had no sign of either premature closure of the ductus arteriosus or pulmonary hypertension. Urine output was normal.

Patient 2

A 27-year-old patient was admitted for observation to the antenatal ward of our hospital in the 20th week of her third pregnancy, because she had a slight, bloody, vaginal discharge.

Her first pregnancy had ended in an abortion at 9 weeks. The second pregnancy ended in preterm labour at 23 weeks gestation; the infant died immediately due to immaturity. From 14 weeks gestation in her third pregnancy she was treated prophylactically with hydroxyprogesterone, administered in an intramuscular dose of 250 mg twice weekly, and with ferrofumarate and folic acid because of anaemia (Hb 9·3 g/dl).

Although the discharge disappeared within a few days after admission, she was kept for observation in view of her obstetric history. As post-

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Department of Obstetrics and Gynecology, RKZ Mariastichting, v Heythuyzenweg 1, 2003 BR Haarlem, The Netherlands
W. DE WIT
I. VAN MOURIK
P. F. WIESENHAAN

Correspondence: W. de Wit, MD, Kerklaan 80, 3731 EJ de Bilt, The Netherlands

prandial glucose levels (lunch tolerance tests, Radder & Terpstra 1980) were repeatedly abnormal, she was treated with insulin after 22 weeks gestation. Ultrasonography revealed no fetal congenital abnormalities. At 27 weeks, ultrasonography showed decreasing cervical length, and as preterm contractions were noted at the same time, it was decided to treat the patient with fenoterol intravenously. At that time the patient was not able to tolerate a higher dose than 0·003 mg/min, but, since this dose did not abolish the premature contractions completely and ultrasonography showed a progressive decrease in cervical length, treatment was extended by adding indomethacin, administered as suppositories in a dose of 3 × 25 mg per day from 28 weeks. As the preterm contractions recurred periodically the dose of fenoterol was increased to 0·006 mg/min and indomethacin was increased to 4 × 25 mg per day from 29 weeks.

A week after initiating indomethacin therapy oligohydramnios had developed. The largest pool of amniotic fluid, which in the weeks before indomethacin treatment had been between 5·3 and 5·7 cm dropped to around 0·9 cm. Filling of the fetal bladder could still be seen on several occasions.

Indomethacin, hydroxyprogesterone and fenoterol therapy were maintained until 31, 32 and 34 weeks, respectively. Three days after stopping indomethacin treatment the largest pool of amniotic fluid measured 2·3 cm, and increased progressively thereafter to 3·2 cm.

All other fetal and maternal measurements were within normal limits until spontaneous delivery at 35 weeks and 6 days. The male infant weighed 2375 g and had no congenital abnormalities. He did well after birth and had no sign of either premature closure of the ductus arteriosus or pulmonary hypertension. Urine output was normal.

Discussion

Prostaglandin synthetase inhibitors, particularly indomethacin, have gained increasing popularity during recent years as tocolytic agents. They have proved to be effective in inhibiting preterm uterine contractions (Niebyl *et al.* 1980; Zuckerman *et al.* 1984), and are easily administered and well tolerated by the mother (Niebyl *et al.* 1980; Zuckerman *et al.* 1984), but they have potential adverse effects on the infant. Prostaglandin synthetase inhibitors have been associated with premature closure of the ductus arteriosus (Arcilla *et al.* 1969), pulmonary hypertension (Manchester *et al.* 1976) and haemorrhagic diathesis in the newborn infant (Itskovitz *et al.* 1980).

Our data show a striking correlation between the period that indomethacin therapy was given and the period that oligohydramnios was present. To our knowledge this is the first report describing the development of oligohydramnios and the normalization of amniotic fluid volume associated with the initiation and termination of indomethacin therapy. The association between the period that indomethacin was given and the period that oligohydramnios was present strongly suggests that the administration of indomethacin caused the oligohydramnios.

Other cases suggesting an association between maternal indomethacin therapy and oligohydramnios were complicated by uteroplacental insufficiency (Cantor *et al.* 1980; Itskovitz *et al.* 1980; Veersema *et al.* 1983), which alone may explain the development of oligohydramnios, and/or it was not established whether amniotic fluid volume was normal before the administration of indomethacin (Itskovitz *et al.* 1980). Prolonged indomethacin administration in primates was associated with oligohydramnios (Novy *et al.* 1974; Manaugh & Novy 1976). However, these cases, but for one, were complicated by the postmaturity syndrome. Thus the circumstances of these earlier reported cases raise doubts about whether indomethacin therapy can be blamed for the development of oligohydramnios.

In our first patient signs of uteroplacental insufficiency were seen, but these occurred after treatment with indomethacin had been discontinued and amniotic fluid volume had normalized, which makes it unlikely that oligohydramnios was caused by uteroplacental insufficiency. Other drugs were given to both patients, but there was no correlation between the period that these were administered and the period of oligohydramnios, so that it is unlikely that the use of these drugs caused the oligohydramnios.

It is attractive to explain the development of oligohydramnios by postulating that indomethacin therapy impaired urine output in these infants, but some evidence would argue against that. Indomethacin therapy is capable of impairing renal flow and urine output, but this is only the case when there are concommitant influences of vasoconstrictors of the renin-angiotensin and/or catecholamine systems on the renal vasculature (Clive & Stoff 1984) (i.e. disorders in which haemodynamic changes occur that lead to an ineffective circulatory volume, such as congestive heart failure). In our two patients there were no signs of such a disorder Also, in both infants filling of the fetal bladder was seen on several occasions during the period of oligohydramnios, suggesting no severe impairment of urine output. In view of those facts, it is unlikely that indomethacin therapy impairs urine output in the fetus; but, in the compromised fetus (when for example there is hypoxia) indomethacin treatment might contribute to the oligohydramnios and the postpartum anuria seen in some cases (Cantor *et al.* 1980; Veersema *et al.* 1983) by impairing the normal prostaglandin-mediated vasodilatory response of the renal vasculature. We can only speculate about the site of action of indomethacin on amniotic fluid production, but in view of our observation, production of amniotic fluid seems at least partially dependant on prostaglandins.

In our opinion prostaglandin synthetase inhibitors are powerful tocolytic agents, which have therapeutic value. Because of their potential harmful effects on the fetus they should be reserved for selected cases, in whom other tocolytics have failed, and preferably for only a short period of time. Indomethacin should not be used in the compromised fetus.

References

Arcilla, R. A., Thilenius, O G. & Ranniger, K. (1969) Congestive heart failure from suspected ductal closure in utero. *J Pediatr* **75**, 74-78

Cantor, B., Tyler, T., Nelson, R. M & Stein, G. H (1980) Oligohydramnios and transient neonatal anuria. A possible association with the maternal use of prostaglandin synthetase inhibiters *J Reprod Med* **24**, 220-223

Chamberlain, P. F., Manning, F. A., Morrison, I , Harman, C. R. & Lange, I R (1984) Ultrasound evaluation of amniotic fluid volume 1. *Am J Obstet Gynecol* **150**, 245-249

Clive, D M. & Stoff, J S. (1984) Renal syndromes associated with nonsteroidal anti-inflammatory drugs. *NEJM* **310**, 563-572

Itskovitz, J., Abramovice, H. & Brandes, J M (1980) Oligohydramnion, meconium and perinatal death concurrent with indomethacin treatment in human pregnancy. *J Reprod Med* **24**, 137-140

Manchester, D., Margolis, H. S & Sheldon, R E. (1976) Possible association between maternal indomethacin therapy and primary pulmonary hypertension of the newborn. *Am J Obstet Gynecol* **126**, 467-469

Manaugh, L C. & Novy, M. J (1976) Effects of indomethacin on corpus luteum function and pregnancy in rhesus monkeys. *Fertil Steril* **27**, 588-598

Niebyl, J R , Blake, D A., White, R D., Kumor, K. M., Dubin, N. H , Robinson, J. C & Egner, P G (1980) The inhibition of premature labor with indomethacin. *Am J Obstet Gynecol* **136**, 1014-1019.

Novy, M J., Cook, M J & Manaugh, L. C (1974) Indomethacin block of normal onset of parturition in primates. *Am J Obstet Gynecol* **118**, 412-416

Radder, J. K & Terpstra, J. (1980) Comparison of postprandial (lunch tolerance) and postglucose (oral glucose tolerance) blood sugar values in pregnancy *Eur J Obstet Gynecol Reprod Biol* **10**, 163-171.

Veersema, D , de Jong, P. A. & van Wijck, J. A M. (1983) Indomethacin and the fetal renal non-function syndrome. *Eur J Obstet Gynecol Reprod Biol* **16**, 113-121.

Zuckerman, H , Shalev, E., Gilad, G. & Katzuni, E (1984) Further study of the inhibition of premature labor by indomethacin II Double-blind study *J Perinat Med* **12**, 25-29.

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The use of a functioning omental flap to drain a recurrent pelvic lymphocyst after radical hysterectomy. Case report

R. J. W. HENRY, A. J. CRANDON

Case report

A 28-year-old woman had a radical hysterectomy and pelvic lymphadenectomy for Stage Ib adenocarcinoma of the cervix in February, 1986. Prophylactic subcutaneous heparin was not used. At the end of the procedure the pelvic peritoneum was closed, a vacuum drain left in each obturator fossa and a T-tube drain in the vagina. The postoperative course was uneventful and she was discharged home after 12 days. Histological examination showed complete excision of the tumour with no lymph node involvement.

At routine follow-up 4 months after operation she complained of urinary frequency and abdominal distension. On examination there was a 10×15 cm cystic mass filling the right side of the pelvis. CT scanning (Fig. 1) confirmed a large right-sided lymphocyst and 650 ml turbid fluid was aspirated under X-ray control.

One month later the patient returned with low abdominal pain and mild fever. There was obvious clinical recurrence of the lymphocyst which now extended out of the pelvis to the level of the umbilicus.

She was admitted again to hospital and a laparotomy was performed via a right paramedian incision. A lymphocyst, measuring 30×25×10 cm, was encountered filling the right side of the pelvis, extending from beneath the bladder base to high in the right iliac fossa (Fig. 2). The left pelvic side wall appeared normal and there was no sign of recurrent tumour.

The greater omentum was dissected from the anterior aspect of the transverse colon. Similarly the omentum was removed from the greater gastric curve to form a 30 cm long omental flap based on an intact right gastro-epiploic vascular pedicle. Care was taken to identify, ligate and divide the left-sided vessels. The caecum was mobilized medially by incising the peritoneum in the right para colic gutter to expose the roof of the lymphocyst. A 10 cm longitudinal incision was made and 800 ml of fluid and debris aspirated; the roof of the lymphocyst was then removed. The lymphocyst cavity was explored deep beneath the bladder and the thickened lining removed by sharp and blunt dissection, with the cyst wall being carefully preserved.

Having first checked the vascular integrity of the distal part of the flap, the omental pedicle was introduced into the cavity of the lymphocyst down to beneath the base of the bladder. A vacuum drain was brought out through a separate incision in the lymphocyst wall and out via a skin incision in the RIF. The omental pedicle was then gently sutured to the wall of the lymphocyst using 2/0 Vicryl (glycolyl-lactyl polyester) suture and the lymphocyst wall was closed loosely with vicryl sutures around the omental pedicle, taking care to avoid tension or constriction of the pedicle. The caecum was restored to a more normal anatomical position by closure of the parietal peritoneum, the appendix was removed and the abdomen closed in a routine manner.

The postoperative course was uneventful: there was minimal drainage from the lymphocyst and the drain was removed after 72 h. The patient was able to return home on the 10th

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Department of Obstetrics and Gynaecology, Westmead Hospital, Westmead, Sydney NSW 2145, Australia

R. J. W. HENRY *Senior Registrar in Obstetrics and Gynaecology*

A. J. CRANDON *Staff Specialist in Gynaecological Oncology*

Correspondence: Mr R. J. W. Henry, Department of Obstetrics and Gynaecology, Poole General Hospital, Poole, Dorset

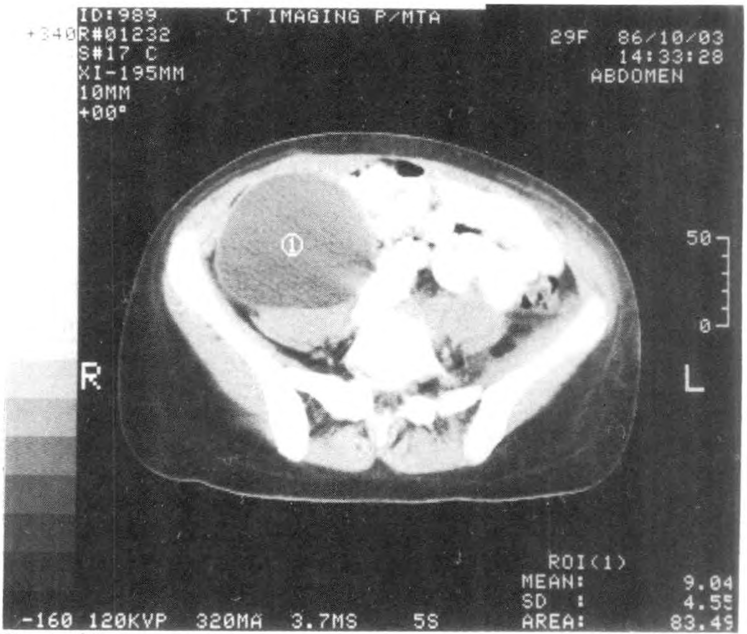

Fig. 1. CT scan of pelvis showing lymphocyst (1), displacing abdominopelvic contents.

postoperative day and she remains well without clinical evidence of recurrence of the lymphocyst 6 months later. A recent bipedal lymphangiogram (Fig. 3) demonstrated extensive collateral lymphatic channels in the right hemipelvis draining superiorly through a large lymphatic channel to the para aortic region at the level of L2/3. These findings would be consistent with lymph drainage via the greater omentum.

Discussion

Pelvic lymphocyst is a surgical complication related to pelvic lymphadenectomy in gynaecological or urological malignancy (Rutledge *et al.* 1959; Choo *et al.* 1986) which has been reported to occur after 1–3% of radical hysterectomies (Sall *et al.* 1979; Powell *et al.* 1981). Lymphocysts are lymph-filled extra-

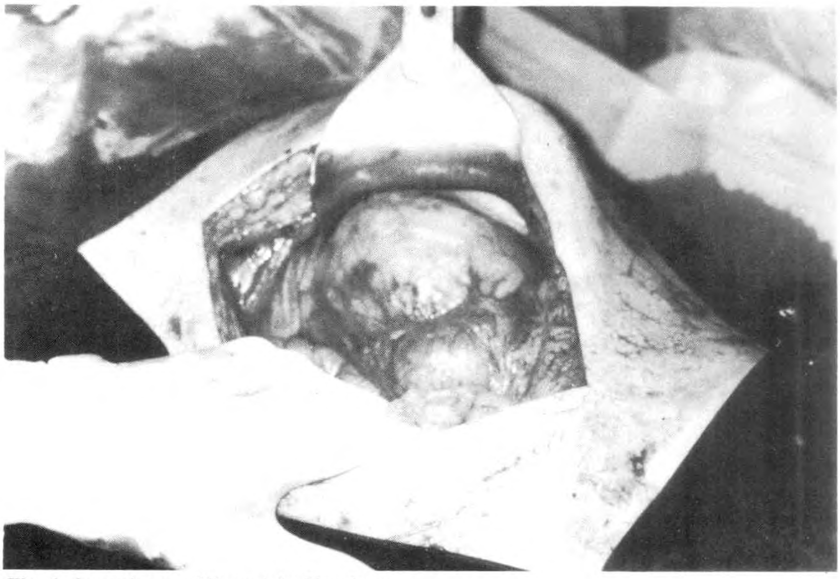

Fig. 2. Lymphocyst filling right iliac fossa.

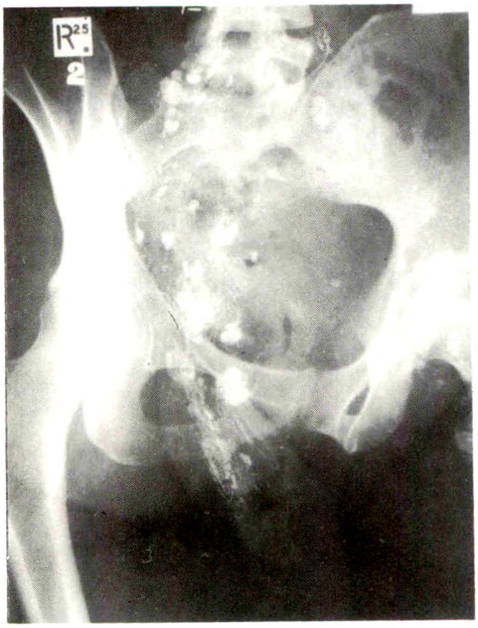

Fig. 3. Lymphogram of pelvis 6 months after the omental pedicle procedure.

peritoneal spaces whose formation may be promoted by several factors: the number of lymph nodes removed, not ligating lymph vessels, the presence of metastatic lymph nodes, post-operative radiation therapy and prophylactic use of anticoagulants (Kragt *et al.* 1986).

The treatment of pelvic lymphocysts is varied. When they are small (3–5 cm) and asymptomatic, continued follow-up and observation are sufficient. When pain or pressure symptoms occur, needle aspiration under ultrasound or X-ray control is a simple and convenient method of drainage. A certain proportion of these cases will recur, however, and require repeated aspiration, thus increasing the risk of infection (Bassinger & Gittes 1975). The range of surgical options available, which include incision and external drainage (Ehrlick & Smith 1977), internal drainage and marsupialization (Geyer & Merrill 1972), antibiotic therapy and internal drainage with packing (Gray *et al.* 1958), indicate the ineffectiveness of these techniques to deal with this problem.

It is our current practice to aspirate symptomatic lymphocysts under ultrasound control once only and if the problem recurs to proceed to internal drainage with an omental pedicle graft as described. In the present patient the lymphocyst was very large, displacing bladder and caecum. A vascularized omental flap based on the right gastro-epiploic vascular arcade was, therefore, interposed into the cavity of the lymphocyst to facilitate drainage.

The use of pedicled omentum in reconstructive and urological surgery is well known but we are unaware of its use in the management of pelvic lymphocyst complicating gynaecological malignancy. The pedicled omental graft is rich in lymphatic and blood vessels and has a large surface area for absorption. Lymph from within the cyst cavity may flow along the wrapped omentum by capillary movement, or alternative paths may be established for lymph to be absorbed. Using this technique the opening of the lymphocyst cavity may remain patent and help to prevent recurrence. The omental flap may be simply fashioned to reach either pelvic side wall and this technique promises to provide an alternative method of internal drainage in cases of difficult or recurrent pelvic lymphocyst.

References

Bassinger, G. T. & Gittes, R. F. (1975) Lymphocyst: ultrasound diagnosis and urological management. *J Urol* **114,** 740-745.

Choo, Y. C., Wong, L. C., Wong, K. P. & Ma, H. K. (1986) The management of intractable lymphocyst following radical hysterectomy. *Gynecol Oncol* **24,** 309-316.

Ehrlick, R. M. & Smith, R. B. (1977) Surgical complications of renal transplantation. *Urology* **10 (Suppl.),** 43.

Geyer, J. R. & Merrill, J. A. (1972) Post-operative pelvic lymphocysts. *J Urol* **108,** 623.

Gray, M. J., Plentyl, A. A. & Taylor, H. C. (1958) The lymphocyst: a complication of pelvic lymphocele dissections. *Am J Obstet Gynecol* **75,** 1059.

Kragt, H., Bouma, J. & Alders, J. G. (1986) Anticoagulants and the formation of lymphocysts after pelvic lymphadenectomy in gynecologic and oncologic operations. *Surg Gynecol Obstet* **162,** 361-364.

Powell, J. L., Burrel, M. O. & Franklin, E. W. (1981) Radical hysterectomy and pelvic lymphadenectomy. *Gynecol Oncol* **12,** 23-32.

Rutledge, F., Dodd, G.D. & Kasilag, F. B. (1959) Lymphocysts: A complication of radical pelvic surgery. *Am J Obstet Gynecol* **77,** 1165-1175.

Sall, S., Pineda, A. A., Calanolg, A., Heller, P. & Greenberg, H. (1979) Surgical treatment of Stage IB and IIA invasive carcinoma of the cervix by radical abdominal hysterectomy. *Am J Obstet Gynecol* **135,** 442-446.

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Emphysematous vaginitis masquerading as carcinoma of the cervix. Case report

J. S. McCALLION, D. E. PARKIN

Case report

A 46-year-old woman was referred from a long-stay psychiatric hospital with a 3-month history of continuous vaginal bleeding. Examination under anaesthesia revealed an indurated, apparently ulcerated cervix, particularly affecting the posterior lip with the induration extending into the posterior fornix and the parametrium. The clinical impression was of a stage IIb invasive cervical carcinoma. A large wedge biopsy from the posterior cervix, endometrial curettings and a cervical smear were submitted for microscopic examination.

Pathology

The cervix was covered by hyperplastic stratified squamous epithelium deep to which was a heavy acute and chronic inflammatory cell infiltrate with moderate fibrosis. The most striking feature was the presence of numerous cystic spaces (Fig. 1), the smaller ones being partially lined by foreign-body type giant cells (Fig. 2). The appearances were those of emphysematous vaginitis.

The curettings consisted of normal secretory phase endometrium and the cervical smear displayed inflammatory features with monilia and trichomonads. No atypical cells were identified.

Discussion

Emphysematous vaginitis is an uncommon, self-limiting condition characterized by multiple gas-filled cysts in the submucosal connective tissue of the upper vagina and the vaginal part of the cervix. The condition is often associated with pregnancy and symptoms are usually mild or absent (Bender & Jeffcoate 1950).

We report here a case of non-puerperal emphysematous vaginitis in which both the clinical history and findings on examination were strongly suggestive of cervical malignancy.

Emphysematous vaginitis was first described by Hugier (1847) since when there has been much speculation about its nature and development. Many pathogenetic hypotheses have been proposed (Gardner & Fernet 1964). Three of the more popular are: (i) that the gas is derived from decomposition of secretions or bacterial debris entrapped in vaginal folds or in occluded glands; (ii) that the cysts originate from dilated lymph spaces; (iii) that atmospheric air is pressurized into interstitial spaces in the submucosa. None of these suggestions is wholly satisfactory. It is now generally accepted that the cysts do not arise from dilated lymph sinuses but rather by gaseous distension of tissue spaces (Bender & Jeffcoate 1950). Each cyst appears to be separate and unconnected to its neighbours and contains gas under pressure (Gardner & Fernet 1964). Because it appears that the gas is continually being absorbed, an endogenous source must exist. The gas has been found to have a high carbon dioxide content (Gardner & Fernet 1964) in keeping with its production by cellular metabolism. They also noted a strong association with trichomonal and *Haemophilus vaginalis* vaginitis, and found that the severity of the emphysematous vaginitis parallelled the severity of the infection. Therefore it may be more than mere coincidence that the subject of this report had a trichomonal infection.

This case was slightly unusual in showing fibrosis and severe inflammation in addition to gas-filled cysts. Persistent trichomonal infection provokes chronic inflammation around para-urethral glands with squamous metaplasia (Riba

Stobhill General Hospital, Glasgow
Department of Pathology
J S McCALLION *Registrar*

Department of Gynaecology
D. E PARKIN *Research Registrar*

Correspondence: D E Parkin, Department of Obstetrics and Gynaecology, North Staffordshire Maternity Hospital, Stoke-on-Trent, Staffs

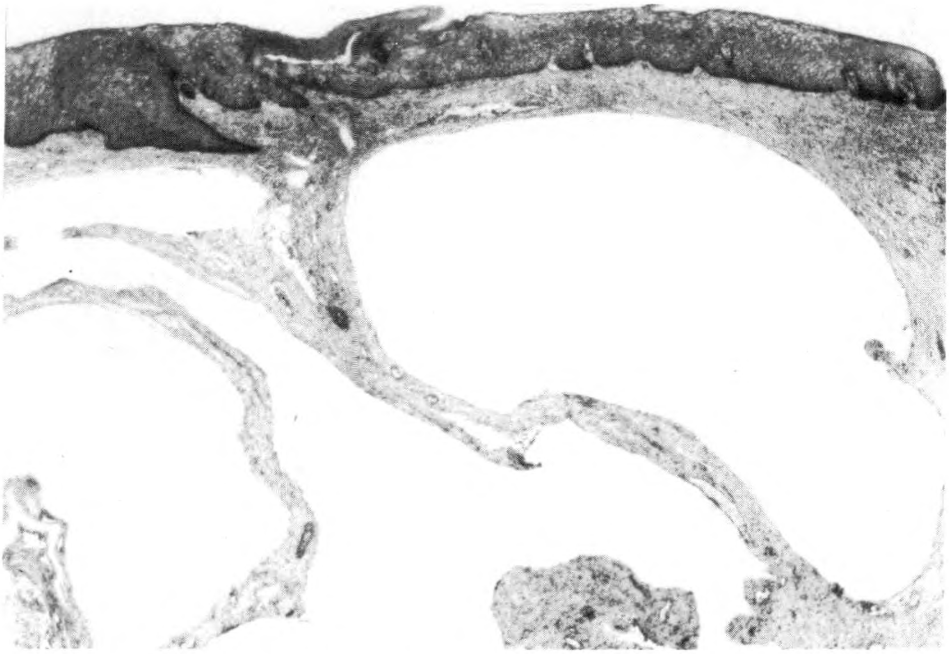

Fig. 1. Large cystic spaces in the submucosal connective tissue (haematoxylin & eosin ×30).

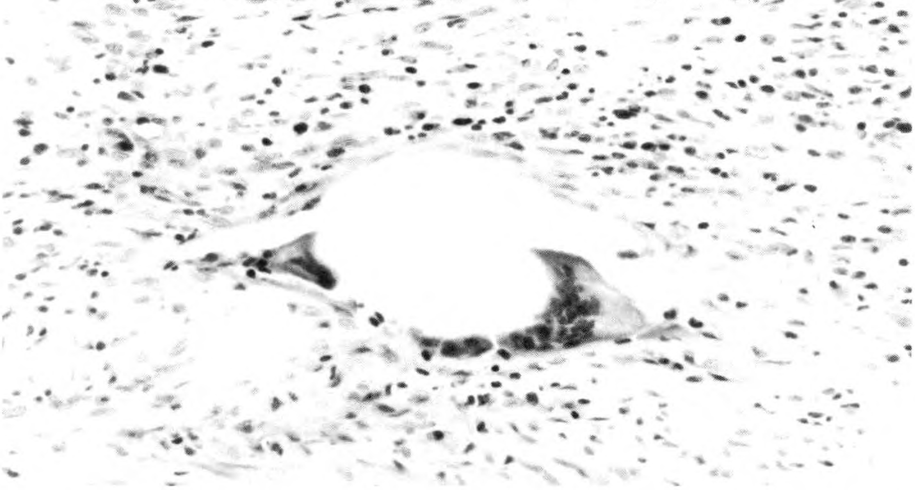

Fig. 2. A small cyst partially lined by foreign body type giant cells (haematoxylin & eosin × 300).

1956) and it seems not unreasonable to suggest a similar response to this protozoon in the cervix. Although most cases of emphysematous vaginitis are of little consequence clinically, our patient demonstrates that when combined with chronic inflammation the condition can mimic cervical carcinoma macroscopically. While the pathogenesis of emphysematous vaginitis remains obscure and the cause of the cervicitis in our patient remains unproven, it is suggested that trichomonal infection is the common factor.

Acknowledgments

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References

Bender, S & Jeffcoate, T N A. (1950) Vaginitis emphysematosa *J Obstet Gynaecol Br Emp* **57**, 432-436.

Gardner, H L & Fernet, P (1964) Etiology of vaginitis emphysematosa *Am J Obstet Gynecol* **88**, 680-694

Hugier, P. C (1847) Memoire sur les kystes de la matrice et sur les kystes folliculaire du vagir. *Mem Soc Chir Paris* 241-376.

Riba, L W (1956) Resistant trichomoniasis in the female. *Am J Obstet Gynecol* **73**, 174-179

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SHORT COMMUNICATIONS

The relation between fetal heart rate and Doppler flow velocity waveform A/B ratio

F. M. Fairlie *Research Registrar, The Royal Maternity Hospital, Glasgow*, J. J. Walker *Senior Lecturer, Department of Obstetrics and Gynaecology, University of Glasgow* & G. D. Lang *Senior Lecturer, Department of Obstetrics and Gynaecology, University of Leicester*

Doppler ultrasound is a non-invasive method of monitoring changes in blood flow velocity. It can be used to study the response of the fetoplacental and uteroplacental circulations to drugs which potentially may alter fetal and maternal blood flow. Giles *et al.* (1987) used continuous wave Doppler to investigate the effect of fluid loading and epidural analgesia on umbilical and uteroplacental flow velocity waveforms before elective caesarean section. They recorded a significant decrease in the ratio of peak systolic to end-diastolic frequencies (A/B ratio) following both fluid loading and epidural analgesia. A fall in A/B ratio is thought to reflect a decline in peripheral resistance (Trudinger *et al.* 1985). Giles *et al.* (1987) concluded that fluid loading and epidural analgesia benefit the fetus by improving placental perfusion. We have embarked on a similar study, investigating the effect of spinal analgesia on umbilical artery flow velocity waveforms. Recordings were taken before and after loading the maternal vascular system with 1 litre of Hartmann's solution and 5, 10 and 15 min after injection of 2·5 ml of 0·5% bupivacaine. In the four patients studied to date, we have been unable to show a consistent increase or decrease in A/B ratio, but three of the four patients showed a change in fetal heart rate (FHR) during the study and we wondered if this could explain the different trends in the A/B ratio. A plot of FHR against A/B ratio for each recording from the four patients showed a significant negative correlation (Pearson's correlation coefficient, $r = -0{\cdot}82$; $n = 20$; $P<0{\cdot}0001$). To investigate this observation further, we recorded umbilical artery flow velocity waveforms during labour, a situation where significant changes in fetal heart rate may occur over short time intervals.

Subjects and methods

Continuous wave Doppler ultrasound was used to record umbilical artery flow velocity waveforms from 34 patients showing decelerations of the FHR during labour. Doppler signals were recorded on two occasions from each patient, between contractions with a FHR of ≥120 beats/min and during contractions when the FHR fell <120 beats/min. The Doppler scanner had a 200 MHz thump filter and all recordings were stored on magnetic tape. The A/B ratio was calculated for a minimum of five waveforms during each recording period and a mean value calculated.

Results

There was a significant negative correlation between the A/B ratio and FHR (Pearson's correlation coefficient, $r = -0{\cdot}61$; $P<0{\cdot}0002$) as shown in Fig. 1.

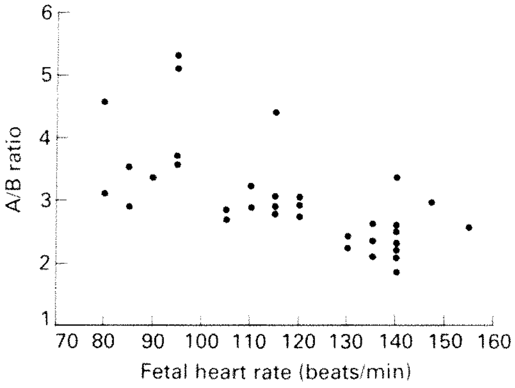

Fig. 1. The relation between fetal heart rate and the A/B ratio of the umbilical artery flow velocity waveform (Pearson's correlation coefficient, $r = -0{\cdot}61$; $P<0{\cdot}0002$).

Discussion

Although we accept that not all factors affecting blood flow in labour may be relevant antenatally, we believe that the correlation between FHR and A/B ratio would explain some of the waveform variation in our spinal study. The relation between FHR and A/B ratio has been noted by other workers (Pearce 1987) and is important to remember when investigating the effect of drug therapy on Doppler flow velocity waveforms. A change in the waveform pattern cannot be automatically attributed to a drug effect and may be due to a variation in other factors such as the FHR.

References

Giles, W B., Lah, F. X. & Trudinger, B. J (1987) The effect of epidural anaesthesia for caesarean section on maternal uterine and fetal umbilical artery blood flow velocity waveforms. *Br J Obstet Gynaecol* **94**, 55-59.

Pearce, J M. (1987) Uteroplacental and fetal blood flow In *Clinical Obstetrics and Gynaecology Vol. 1* Baillière Tindall, Eastbourne, pp 157-184

Trudinger, B. J , Giles, W. B , Cook, C M., Bombardieri, J. & Collins, L (1985) Fetal umbilical artery flow velocity waveforms and placental resistance. clinical significance. *Br J Obstet Gynaecol* **92**, 23-30.

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Prediction of small-for-gestational-age infants using a specially calibrated tape measure

Matthews Mathai *Reader in Obstetrics and Gynaecology, Christian Medical College Hospital, Vellore 632 004, India*

A simple method of screening for small-for-gestational-age (SGA) infants uses the comparison of fundal height measurements with standard fundal height charts for that population (Belizan *et al.* 1978; Calvert *et al.* 1982; Mathai *et al.* 1987). This method has satisfactory sensitivity and specificity and is easily understood by trained health personnel. If used correctly, the combination of fundal height measurements and perinatal risk factors can have a predictive power as high as any of the other more sophisticated techniques used in the prediction of SGA infants (Villar & Belizan 1986). However, in developing countries, figures and charts have less meaning for the relatively untrained health worker at the village level. With this in mind, a specially calibrated tape measure was designed for the prediction of SGA infants.

Patients and methods

The fundal height chart used in the Department of Obstetrics and Gynaecology, Christian Medical College Hospital, Vellore, India, is based on serial measurements obtained from 250 consecutive women with normal pregnancies who were delivered at term (Mathai *et al.* 1987). A regression equation, fundal height $(\text{cm}) = 4{\cdot}66093+(0{\cdot}74468\times\text{gestation in weeks})$ was obtained from these data and a regression line was drawn. Since a 4-week lag in fundal height is a criterion for the clinical prediction of SGA, any measurement of fundal height falling 3 cm or more below the regression line for that gestation was considered predictive of SGA. These 'cut-off levels' of fundal height calculated for 2-week intervals from 20 to 40 weeks gestation were marked on a tape measure. Each calibration was labelled as the corresponding gestation in weeks for that level.

This preliminary study was done in the antenatal clinics of Obstetric Unit II at the Christian Medical College Hospital, Vellore, between March 1985 and January 1986. The specially calibrated tape measure was used during routine examination by medical students and junior house officers to screen for SGA. Each observer had been instructed by the author on the standard technique of measurement. Symphysial fundal height was noted directly on the tape measure and any measurement of fundal height falling at or below the 'cut-off level' for that gestation was considered predictive of SGA. These diagnostic predictions were compared with actual birthweights.

Results

The results of screening 253 women with low-risk pregnancies for SGA are summarized in

Table 1. Prediction of small-for-gestational-age infants in 253 low-risk pregnancies

Birthweight	Correct diagnosis	Incorrect diagnosis
< 10th centile	23	7
≥ 10th centile	177	46

Table 1. The sensitivity and specificity rates were 77% and 79% respectively.

Discussion

The results of this preliminary study of the use of the specially calibrated tape measure in predicting SGA are encouraging. These results are comparable with those reported with the use of standard fundal height charts (Belizan *et al.* 1978; Calvert *et al.* 1982; Mathai *et al.* 1987). The specially calibrated tape is less expensive, equally reliable and simpler to use than the standard fundal height charts. The use of similar specially calibrated tape measures for the diagnostic prediction of SGA may be easily taught to health workers with minimal training. Early prediction of SGA and referral to larger centres for appropriate perinatal care may eventually reduce the perinatal mortality and morbidity associated with this condition.

References

Belizan, J. M., Villar, J., Nardin, J C., Malamud, J. & Sainz de Vicuna, L (1978) Diagnosis of intrauterine growth retardation by a simple clinical method measurement of uterine height *Am J Obstet Gynecol* **131**, 643-646

Calvert, J P, Crean, E. E., Newcombe, R. G & Pearson, J. F. (1982) Antenatal screening by measurement of symphysis-fundus height *Br Med J* **285**, 846-849.

Mathai, M., Jairaj, P. & Muthurathnam, S (1987) Screening for light-for-gestational-age infants a comparison of three simple measurements *Br J Obstet Gynaecol* **94**, 217-221.

Villar, J & Belizan, J M (1986) The evaluation of the methods used in the diagnosis of intrauterine growth retardation *Obstet Gynecol Surv* **41**, 187-199

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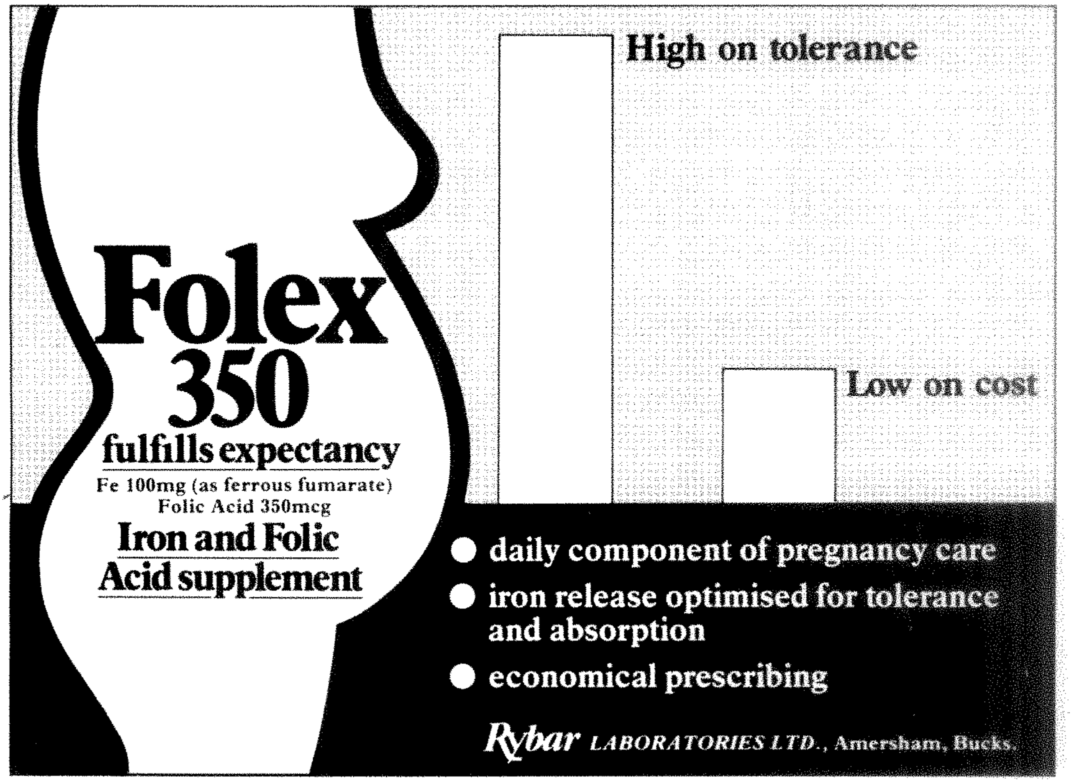

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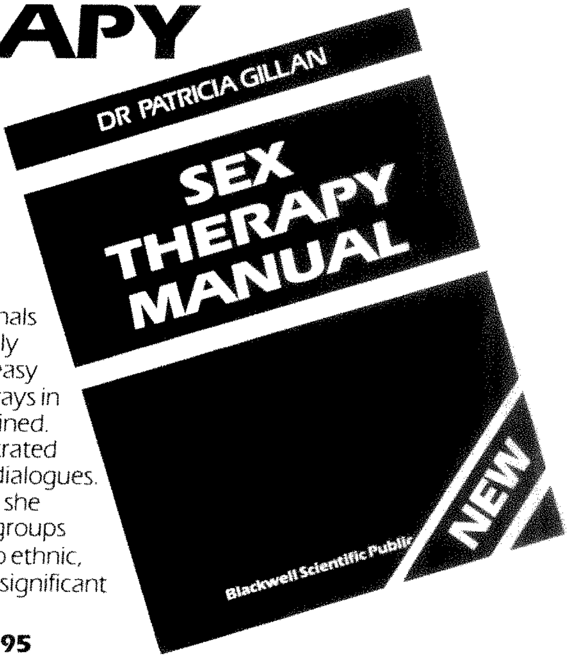

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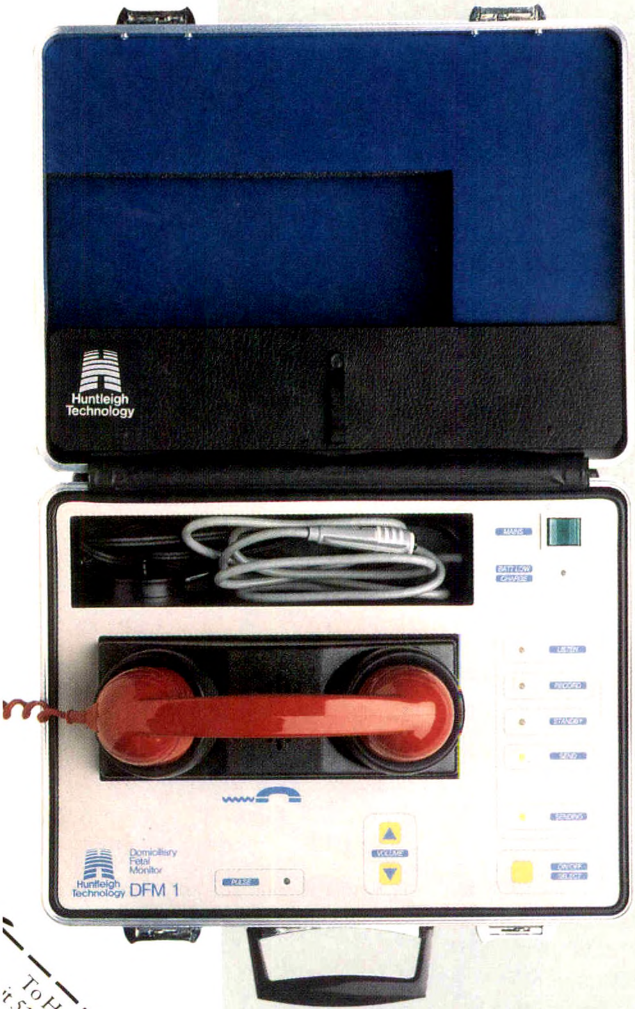

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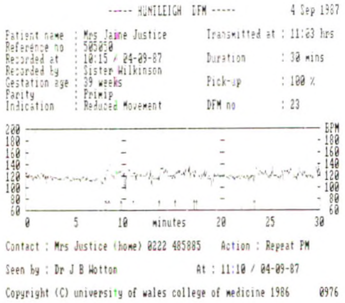

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----- HUNTLEIGH  DFM -----                  4 Sep 1987

Patient name   : Mrs Jaine Justice        Transmitted at : 11:23 hrs
Reference no   : 505050
Recorded at    : 10:15 / 04-09-87         Duration       : 30 mins
Recorded by    : Sister Wilkinson
Gestation age  : 39 weeks                 Pick-up        : 100 %
Parity         : Primip
Indication     : Reduced Movement         DFM no         : 23
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200
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160
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120
100
80
60
BPM
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5
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British Journal of Obstetrics and Gynaecology
March 1988, Vol. 95, pp. 315–317

CORRESPONDENCE

The effect of fetal heart rate on umbilical artery flow velocity waveforms

Dear Sir,
I agree with Mires *et al.* [*Br J Obstet Gynaecol* (1987) **94,** 665–669] that it is important to take fetal heart rate (FHR) into account when analysing blood flow velocity waveforms, especially because there is a clear inverse relation between FHR and indicators of peripheral vascular resistance, such as pulsatility index (PI), A/B ratio and resistance index (RI). I was surprised that the authors were unable to find any published study on this subject. Our group has reported on the relation between FHR and PI in the fetal descending aorta (van Eyck *et al.* 1985*a,b*) and also in the umbilical and fetal internal carotid artery (van Eyck *et al.* 1986*a,b,c,d*). We are looking forward to the studies that are currently being undertaken by the group in Dundee in order to compare their results with ours (van Eyck *et al.* 1987, 1988; van den Wijngaard *et al.* 1988). Mires *et al.* (1987) do not discuss the importance of the degree of the inverse relation which might give more information about the peripheral vascular resistance than a single PI measurement, even when it is corrected for FHR (140 beats/min). When the FHR is low, the time that the blood flow during diastole is submitted to the slackening force of the peripheral vascular resistance will be longer, resulting in a reduced end diastolic velocity (EDV) and averaged velocity (AV) (van Eyck 1985*b*). According to the formula of Gosling & King (1975),

$$\mathrm{PI} = \frac{\mathrm{PV}-\mathrm{EDV}}{\mathrm{AV}},$$

a lower FHR will result in a raised PI.

The peripheral vascular resistance in various fetal vessels, e.g. descending aorta, umbilical artery, internal carotid artery and various conditions, e.g. normal growth, intrauterine growth retardation and fetal behavioural states, which is responsible for this slackening force, will therefore determine the degree of this inverse relation (unpublished observations).

J. van Eyck
Academic Hospital Rotterdam Dijkzigt
Erasmus University Rotterdam
Dr Molewaterplein 40
3015 GD Rotterdam
The Netherlands

References

Gosling, R. G. & King, D. H (1975) Ultrasound angiology. In *Arteries and Veins* (Marous, A. W. & Adamson, L.), Churchill Livingstone, Edinburgh, pp. 61-98.

Mires, G., Dempster, G. S., Patel, N. B. & Crawford, J. W (1987) The effect of fetal heart rate on umbilical artery flow velocity waveforms *Br J Obstet Gynaecol* **94,** 665-669.

van Eyck, J., Wladimiroff, J. W., Noordam, M J., Tonge, H. M. & Struyk, P. (1985*a*) The blood flow velocity waveform in the fetal descending aorta relative to fetal behavioural state in normal pregnancy at 37–38 weeks. *Abstracts of the International Workshop on Developmental Neurology of the Fetus and Preterm Infant* Groningen, The Netherlands.

van Eyck, J., Wladimiroff, J. W., Noordam, M. J., Tonge, H. M & Prechtl, H F. R. (1985*b*) The blood flow velocity waveform in the fetal descending aorta; its relationship to fetal behavioural states in normal pregnancy at 37–38 weeks. *Early Hum Dev* **12,** 137-143.

van Eyck, J., Noordam, M J., van der Wijngaard, J. A. G W., Wladimiroff, J W. & Prechtl, H F R. (1986*a*) Behavioural states and blood flow in the human fetus. *Abstracts of the International Symposium on Fetal Physiology—Cellular and Systems Approaches, 19.* vancouver Island, Canada.

van Eyck, J., Noordam, M. J., van der Wijngaard, J. A. G. W , Wladimiroff, J. W & Prechtl, H. F R. (1986*b*) Behavioural states and blood flow in the human fetus. *Abstracts of the XIII Annual Conference of the Society for the Study of Fetal Physiology.* Banff, Canada.

van Eyck, J., Wladimiroff, J. W., Noordam, M J., Tonge, H. M. & Prechtl, H. F. R (1986*c*) The blood flow velocity waveform in the fetal descending aorta; its relationship to behavioural states in the growth retarded fetus at 37–38 weeks of gestation. *Early Hum Dev* **14**, 99-107.

van Eyck, J., Wladimiroff, J. W., van den Wijngaard, J. A. G. W., Noordam, M. J. & van Kooten, C (1986*d*) Fetal blood flow in relation to fetal behavioural states *Abstracts of the International Conference on Current Status and Future Developments in Fetal Cardiovascular Echography*, 61-62, Rotterdam, The Netherlands.

van Eyck, J., Wladimiroff, J W , van den Wijngaard, J. A. G. W , Noordam, M. J. & Prechtl, H. F R. (1987) The blood flow velocity waveform in the fetal internal carotid and umbilical artery; its relation to fetal behavioural states in normal pregnancy at 37–38 weeks. *Br J Obstet Gynaecol* **94**, 736-741.

van Eyck, J., Wladimiroff, J. W., Noordam, M. J., van den Wijngaard, J. A. G. W. & Prechtl, H. F. R. (1988) The blood flow velocity waveform in the fetal internal carotid and umbilical artery; its relation to fetal behavioural states in the growth retarded fetus at 37–38 weeks gestation. *Br J Obstet Gynaecol* **95** (in press).

van den Wijngaard, J. A. G. W., van Eyck, J., Noordam, M. J., Wladimiroff, J. W. & van Strik, R (1988) The Doppler flow velocity waveform in the fetal internal carotid artery with respect to fetal behavioural states; a longitudinal study. *Biology of the Neonate* (in press).

Authors' reply

Dear Sir,

We feel that J. van Eyck has misunderstood the main points of our paper. These were first, that FHR has a marked effect on the qualitative indices used to analyse umbilical artery blood flow and second, that high ratios may be reflecting fetal bradycardia and may not be indicative of increased placental resistance. His extensive list of publications was unhelpful in reference to our paper. Although two of the references have been published, umbilical artery blood flow is not discussed. Several of the references are abstracts from international symposia which are not widely available in Britain, and three have yet to be published. We have, however, read van Eyck *et al.* (1987) after it was published and were interested to note that behavioural states may be another factor influencing fetal blood flow.

Gary Mires
Registrar
Jane Dempster
Research Registrar
Ninewells Hospital
Dundee DD2 9SY

Dear Sir,

Recently Mires *et al.* (1987) reported on the relation between fetal heart rate (FHR) and A/B ratio in umbilical artery velocity waveforms. The authors stated that they had been unable to find any published data on this question, but there have been several previous reports for both fetal umbilical and aortic waveforms (van Eyck *et al.* 1985; Thompson *et al.* 1986; Mulders *et al.* 1986; Lingman & Marsal 1986). These groups have used variously the A/B ratio, pulsatility index (PI) or Pourcelot ratio (PR or RI), but these indices are all closely related (Thompson *et al.* 1988). Thompson *et al.* (1986) found virtually no correlation between umbilical artery A/B values and FHR ($r = -0{\cdot}11$ for 56 normal patients). Mulders *et al.* (1986) found a significant negative correlation between the umbilical artery PI and FHR in 13 of 19 patients. van Eyck *et al.* (1985) considered the relation between PI, fetal state (1F or 2F) and FHR in the descending aorta. The aortic PI was state dependent and varied inversely with FHR in state 2F. Lingman & Marsal (1986) reported correlation coefficients between the PI and FHR of −0·43 for the descending aorta and −0·22 for the abdominal aorta.

These results indicate a weak association between umbilical artery waveforms and FHR, but they also indicate the importance of defining methodological conditions in Doppler studies. Mires *et al.* (1987) estimated the FHR and A/B values visually from single waveforms. No averaging or other processing was used to obtain representative waveforms and minimize errors *before* calculating the waveform indices. Under these conditions the sort of variability between single observations shown in their Fig. 3 will be maximized rather than minimized. Mires *et al.* (1987) suggested adjusting all A/B values to a 'standard' heart rate of 140 beats/min using the equation A/B ratio = observed A/B ratio − 0·014 (140 − observed FHR). This leads to 'corrections' in A/B values which are very small (e.g. ±0·28 for a FHR change of ±20 beats/min). A normal A/B value at 38 weeks could range from 2·21 (50th centile) to 2·80 (95th centile). Thus the magnitude of the correction factor is small (approximately 10%) in relation to the A/B value. It is not larger than the magnitude of the errors to be expected in calculated waveform indices (Thompson *et al.* 1988).

The effect of FHR on the waveforms is stronger in the aorta than in the umbilical artery and is related to fetal state. It seems likely that this will be found to be due to changes in the peripheral resistance with fetal activity. There are a number of fetal and placental factors which determine both the FHR and the A/B ratio. It is simplistic to treat the effect of FHR on the A/B ratio as an artefact which can be eliminated. The authors themselves acknowledge this in the Discussion where they state that the range of A/B ratios at low heart rates in labour is greater than could have been expected by FHR alone.

For the reasons expressed in the above two paragraphs we feel that it is most inappropriate for A/B values to be adjusted to a 'standard' heart rate of 140 beats/min. The umbilical artery velocity waveforms provide a method of recognition of changed circumstances in the fetal vascular system. The pattern of change in the A/B values in the longer term is more important than individual absolute values.

R. S. Thompson
Research Officer
B. J. Trudinger
Associate Professor
C.-M. Cook
Technical Officer
Department of Obstetrics and Gynaecology
The University of Sydney at Westmead Hospital
Westmead, NSW 2145
Australia

References

Lingman, G. & Marsal, K (1986) Fetal central blood circulation in the third trimester of normal pregnancy. A longitudinal study. *Early Hum Dev* **13**, 151-159

Mires, G., Dempster, J., Patel, N. B. & Crawford, J. W. (1987) The effect of fetal heart rate on umbilical artery flow velocity waveforms *Br J Obstet Gynaecol* **94**, 665-669.

Mulders, L. G. M., Muijsers, G. J. J. M., Jongsma, H. W , Nijhuis, J. G. & Hein, P. R. (1986) The umbilical artery blood flow velocity waveform in relation to fetal breathing movements, fetal heart rate and fetal behavioural states in normal pregnancy at 37 to 39 weeks. *Early Hum Dev* **14**, 283-293.

Thompson, R. S., Trudinger, B. J & Cook, C M. (1986) A comparison of Doppler ultrasound waveform indices in the umbilical artery. 1. Indices derived from the maximum velocity waveform. *Ultrasound Med Biol* **12**, 835-844

Thompson, R S., Trudinger, B. J. & Cook, C. M. (1988) Doppler ultrasound waveform indices. A/B ratio pulsatility index and Pourcelot ratio. *Br J Obstet Gynaecol* (in press).

van Eyck, J., Wladimiroff, J. W., Noordam, M. J., Tonge, H. M. & Prechtl, H. R. F (1985) The blood flow velocity waveform in the fetal descending aorta: its relationship to fetal behavioural states in normal pregnancy at 37–38 weeks. *Early Hum Dev* **12**, 137-143.

Authors' reply

Dear Sir,

In reply to the letter from R. S. Thompson *et al.*, our findings differ from those of Thompson *et al.* (1986). We have found a significant correlation between umbilical artery A/B ratios and FHR both antenatally and during labour. As pointed out in their letter, other workers have found a similar relation to exist between flow velocity waveforms in various fetal vessels and FHR.

It is very apparent from the waveform patterns that at slower FHR, a lower end diastolic frequency is obtained before the next cardiac impulse travels down the vessel. Conversely at faster FHR a higher end diastolic frequency is obtained because the cardiac impulses are occurring more frequently. We have shown this in practice. We agree that if the FHR does not differ greatly from the norm then the correction factor will be less important. However, in the small number of patients with slow or rapid heart rates, false negative or false positive results could occur. Although such cases will be small in number compared with the total cases tested, they could well comprise a significant number of compromised fetuses and thus, like so many previous tests, lead to false complacency or perhaps more commonly unnecessary interference.

We are aware that other sources of error exist and that many factors may affect the A/B ratio obtained. Our paper shows that the effect of FHR is a factor which has been identified and can be minimized by allowing a correction factor to be made. We feel that this is an advantage, not a disadvantage.

We agree entirely with the concluding comment from R. S. Thompson in that long-term changes in the A/B values are more important than individual absolute values.

Gary Mires
Registrar
Jane Dempster
Research Registrar
Ninewells Hospital
Dundee DD2 9SY

British Journal of Obstetrics and Gynaecology
March 1988, Vol. 95, pp 318–320

BOOK REVIEWS

Prevention of Preterm Birth: New Goals and New Practices in Prenatal Care edited by E. Papiernik, G. Bréart & N. Spira. Inserm, Institut National de la Recherche Medicale, 101 Rue de Tolbiac, 75654 Paris, Cedex 13, France, 475 pages with figures and tables, FF 200

Preterm birth is such a disadvantage for the neonate, whether in a singleton or multiple birth, that it is not surprising that so much endeavour has been devoted to its prevention. Interpretation of changes in preterm delivery rates is difficult, as some countries have no routinely collected data, and in others, such as the USA, missing data about gestational age occurs most frequently in the social groups and geographical areas where the problem is thought to be greatest. In France, there does seem to have been a greater reduction in preterm delivery rates than other countries have experienced, and there is of course great interest in French medical and social interventions and their evaluation. These were described and discussed in detail, together with papers from many other countries, at an important symposium in Evian in 1985, of which this book is a report. Papers both in English and in French are included; but this should not deter Anglophones as there are summaries in English throughout and some French authors have shamed us by writing in perfect English.

The main outcome measure considered is preterm delivery itself, but low birthweight, perinatal mortality, uptake of services offered, and their cost-effectiveness, are also discussed. The question of whether interventions should be offered to all women or only to those at high risk of preterm labour is an interesting one, and it is paradoxical that although so much pioneering work on detection of risk was done by Papiernik in France, Rumeau-Rouquette considers the risk approach to have been a relative failure at the national level. Her thoughtful summary chapter makes interesting reading.

Most of the interventions described in this book are social or medicosocial in character, which is not surprising in view of the paucity of evidence for the effectiveness of purely medical treatments such as drugs, cerclage etc. Measures including home visits by midwives or by family workers, antenatal education and modification of patterns of work, are proposed in studies from the USA, France (including Martinique), Australia and Britain. Many of the studies described were not yet complete, but it is well worth reading the reports of their progress and planning. The dilemma as to whether all studies should be controlled, and the problems of convergence and contamination that may occur even if they are, are well ventilated.

The book is well organized into sections and should appeal particularly to obstetricians with an interest in ascertaining the value of their routine practices, in teasing out just what it is that is having a beneficial or negative effect, and in what happens to the women who cannot or will not accept any medical measures but may have social or economic problems needing a different approach.

Marion Hall

Current Therapy in Surgical Gynecology edited by Celson-Ramon Garcia, John J. Mikuta & N. G. Rosenblum. B. C. Decker, Inc., Toronto, Philadelphia, 1987, 237 pages with figures and tables, £36.00

This book is a particular pleasure to read, not just for its content, but also for its language. The editors have ensured that all the contributed chapters are written in a clear and economic style, avoiding the infelicities of expression which are sometimes evident in American medical texts.

The introductory section on pre-operative assessment and postoperative care provides ample but compact guidance. Included is an impressive and salutary table listing 51 complications which can result from central venous catheterization, and 20 adverse metabolic consequences of intravenous hyperalimentation. There is a good account of septic shock and its management.

In the core of the book are the chapters dealing consecutively with the operative procedures (major and minor) of gynaecological practice, and they breathe a wealth of experience. Every young gynaecologist should read A. C. Richardson's account of abdominal hysterectomy, with its insistence on the finesse of good technique—fine needles and suture materials, gentle accurate dissection and, above all, respect for tissue His results speak for themselves 1000 hysterectomies with a mean hospital stay of 3·2 days!

Some contemporary controversies are also covered. One contributor presents clearly and convincingly the case against ovarian ablation at the time of hysterectomy in the woman over 40. Another argues the case for selective use of subtotal hysterectomy in settings where cervical cytology and colposcopy are available. There are presented comparative trials of Hulka clip versus bipolar diathermy for laparoscopic sterilization, concluding that bipolar diathermy is the procedure of choice. This the reviewer would endorse but is less than happy with the declaration that the Manchester operation 'is an archaic procedure, of historic interest only'. Such sacrilege!

The alternatives and contraindications to surgery are also discussed where appropriate in a very balanced way. There is a satisfactory index but no references Overall the book is highly commended.

Philip R. Myerscough

Diagnostic Imaging of Infertility edited by Alan C. Winfield & Anne Colston Wentz. Williams & Wilkins, Baltimore, 1987, 237 pages with figures and tables, £39.00

This is mainly a text on hysterosalpingography but with an introductory chapter on clinical aspects of infertility and concluding chapters on ultrasonography and on investigation of the male to try to give the book credibility as a general account of diagnostic imaging in the management of the subfertile couple. The chapter on clinical aspects is brief and pitched at a level appropriate for undergraduates; it will not be found illuminating by practising gynaecologists The eight chapters on hysterosalpingography are detailed, comprehensive and well illustrated. There is an occasional tendency to repetition and to inconsistency—it is difficult to reconcile, for example, the statement that hysterosalpingography is 'non-invasive' with the description of the 11 reported deaths attributed to the procedure (five from embolism, six from infection). Discussion of the merits of hysterosalpingography in comparison to those of laparoscopy for tubal assessment appears inappropriately late in the text; comparison with hysteroscopy to assess the uterine cavity is very sketchy. The chapters on ultrasonography in gynaecology and in early pregnancy are competent but some of the ultrasonograms are of disappointing quality. Recent uses of ultrasound to monitor ovulation induction and to aid egg retrieval could have received more attention

For those with a special interest in hysterosalpingography this book should prove useful for reference. It was, I suspect, written more for radiologists than gynaecologists; it will certainly appeal more to the former group.

J. Neilson

Ovarian Malignancies: Diagnostic and Therapeutic Advances (Clinical Obstetrics and Gynaecology edited by M. Steven Piver. Churchill Livingstone, Edinburgh, 1987, 302 pages with figures and tables, £45.00

The present interest in ovarian cancer is demonstrated by the fact that there are now several good books available on this topic. There is, however, a good reason for advocating that gynaecologists add this particular volume to their library, in that this book not only gives a comprehensive review of the state of the art in the management of ovarian cancer at the present time, but also devotes considerable attention to dealing with specific and important aspects of these tumours. For instance there is an increasing need to advise patients on the risk of developing ovarian cancer and this topic is discussed in detail both in a chapter on the epidemiology of ovarian cancer, and in one devoted solely to hereditary factors. A minor criticism of the latter chapter is the complicated diagrams showing family trees which, by being too detailed, are difficult to follow. Another important topic is borderline malignancy, as most gynaecologists are aware there are difficulties in deciding on the management of borderline ovarian carcinoma when it has spread beyond the ovary. In this regard the chapter devoted to borderline tumours includes recent data showing that invasive peritoneal deposits appear to be associated with a poor prognosis and therefore adjuvant chemotherapy should be given regardless of the pathology of the primary lesion. For other cases of borderline tumours chemotherapy has not been shown to be of any efficacy This book is of particular value to gynaecologists needing a reference work in order to deal with the rare non-epithelial ovarian tumours, for example germ cell, sex cord-stromal tumours and ovarian sarcomas. These are dealt with in great detail covering several chapters

For each tumour pathology, diagnosis and treatment are included and special attention is given to the extent of initial surgery, as for example in germ cell tumours in young women, with the advent of modern chemotherapy, both survival and fertility can be preserved. Radiotherapy has little place even in dysgerminoma despite its radiosensitivity because of the risk of infertility. For the common epithelial tumours one chapter deals with the staging and treatment of early cases, i.e. stages I and II, including surgery, chemotherapy and radiotherapy both external and intraperitoneal. The author's approach is that of a critical analysis of past papers so that the reader is helped to determine for him or herself the value of present therapy. Following radical surgery the benefit of adjuvant chemotherapy or radiotherapy in stage I carcinoma remains unproven but is advocated for those at greatest risk of recurrence, i.e. those with poorly differentiated tumours. The same critical approach is used in chapters on the value of second look surgery, radiation therapy and chemotherapy for advanced epithelial ovarian carcinoma. In addition, there is an excellent well-illustrated chapter on the pathology of ovarian tumours and further chapters on diagnosis, tumour markers and radiological techniques.

In summary, this is overall an excellent critique of present day management of ovarian tumours, both the common epithelial and the rarer non-epithelial tumours, which should prove helpful to all gynaecologists. I strongly recommend it.

Joanna Lambert

Books received some of which may be reviewed at a later date

Caesareans: An Explanation and Preparation by Elliot Philipp. Sidgwick & Jackson, London, 1988, 148 pages, £12.95

The Contraceptive Ethos (Philosophy and Medicine 27) edited by Stuart F Spicker, William B Bondeson & H Tristram Engelhardt Jr. D. Reidel Publishing Company, Dordrecht, 1987, 254 pages, £32.95

Protocol for High-Risk Pregnancies edited by John T. Queenan & John C. Hobbins. Medical Economics Books, Oradell, NJ, 1987, 449 pages, £22.50+£1.50 postage

Bacterial Vaginosis by W. I. van de Meyden. Van Gorcum, The Netherlands, 124 pages illustrated, Dfl 35

Cervical Cancer: And How To Stop Worrying About It by Judith Harvey, Sue Mack & Julian Woolfson. Faber & Faber Ltd, London, 1988, 88 pages, £3.95

The Hypertensive Disorders of Pregnancy (Report of a WHO Study Group, Technical Report Series 758) World Health Organization, Geneva, 1986, 114 pages, Sw. fr. 16

Directions to contributors

All papers should be sent to The Editor *British Journal of Obstetrics and Gynaecology*, 27 Sussex Place, Regent's Park London NW1 4RG. Papers received are assumed to have been submitted exclusively to the *British Journal of Obstetrics and Gynaecology* and *all* authors must give signed consent to publication in a letter sent with the manuscript. The Editor will decide on the time of publication and retains the usual right to modify the style and length of a contribution, major changes will be agreed with the author(s).

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Two copies of the manuscript and illustrations should be sent. Manuscripts should be typed double spaced on one side of the paper, with wide margins. The names of author(s) and their appointment(s) and addresses at the time of preparation of the manuscript should be given. Authors are advised to keep a copy of all manuscripts, as no responsibility can be accepted for loss.

Reports of original work should usually be arranged in the conventional order of summary, introduction, methods, results, discussion, acknowledgments and references, with suitable headings for each part. Two further sub-divisions, with appropriately less significant headings, can be used, the third order heading runs on with text at a paragraph opening. Results may be presented in the text, in tables and/or figures, but the text should, in general, comment on rather than repeat information in tables. The summary should contain a factual account of the methods and results in not more than 150 words, rather than a description of the subject of the paper and the opinions of the author(s).

Case reports and short communications do not require a summary or introduction. Short communications should not exceed 600 words and contain no more than one table or figure.

Tables and figures
Tables and figures should be separate from the text, with their positions indicated in the text margin. Both are numbered with arabic numerals. Colour illustrations are allowable only in special circumstances and the author will be expected to meet the cost of reproduction.

Figures should be marked on the back (light in pencil) with the name(s) of the author(s), the figure number, and the top indicated. Each should have a descriptive legend typed on a sheet separate from the figure. Photographs should be unmounted glossy bromide prints of good contrast.

Figures consist of all material which cannot be set in type, such as photographs, line drawings, etc. Tables are not included in this classification and should not be submitted as photographs. Original X-ray films should not be sent—glossy prints must be submitted.

Line drawings should be on white board, arranged to conserve space, and should allow for reduction to 65 mm (single column) or 134 mm (double column).

Typewritten lettering should not be used on illustrations and explanations should appear in the legend not on the figure itself.

The identity of patients in illustrations should be concealed by masking the face or eyes, or written permission for publication from the patient or the parent or guardian must be supplied.

Units and abbreviations
Measurements should be expressed in SI units with the exception of haemoglobin (g/dl) and blood pressure (mmHg). If the original observations were recorded in other units this should be stated, together with the appropriate conversion factors. Standard abbreviations, without punctuation, are used. *Units, Symbols and Abbreviations* (1977) published by the Royal Society of Medicine provides a useful guide. Abbreviations are used sparingly and only if a lengthy name or expression is repeated frequently throughout the manuscript. Words must appear in full on first appearance in both summary and text, followed by the abbreviation in parenthesis.

Drugs are described by their official names but trade names should be indicated in brackets the first time a drug is quoted in the main text.

Statistics
Authors should describe clearly the design of their investigation and the source of the data. All statistical methods should be specified so that it is clear which was used where. Papers omitting this information may be returned without review. The basic principle to follow is to supply sufficient information about the design and methods of analysis to allow the research to be repeated by someone else.

Some points of detail to note are:

(1) It is not acceptable to present the results of a statistical analysis solely by a *P* value—actual results such as means or proportions should always be given, along with the test statistic.
(2) The use of confidence intervals is encouraged.
(3) The symbol ± should not be used when presenting SE or SD. Presentation such as 'the mean was 14·2 (SD 3·2) mg' is preferred.
(4) When paired comparisons are made it is desirable to indicate the variability of within-pair differences.
(5) Unusual methods of analysis should be described and/or referenced.

Authors are referred to the general statistical guidelines of Altman *et al* (1983) for advice about the presentation and interpretation of the statistical aspects of their research.

Altman, D G, Gore, S M, Gardner, M J & Pocock, S J (1983) Statistical guidelines for contributors to medical journals. *Br Med J* **286**, 1489–1493.

Human experiments
Manuscripts should contain a statement that the work was approved by the ethics committee of the institution in which it was done and that subjects gave informed consent to the work. The editors reserve the right to reject papers if they consider the ethical justification to be questionable.

References
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Volume 95, Number 4, April 1988

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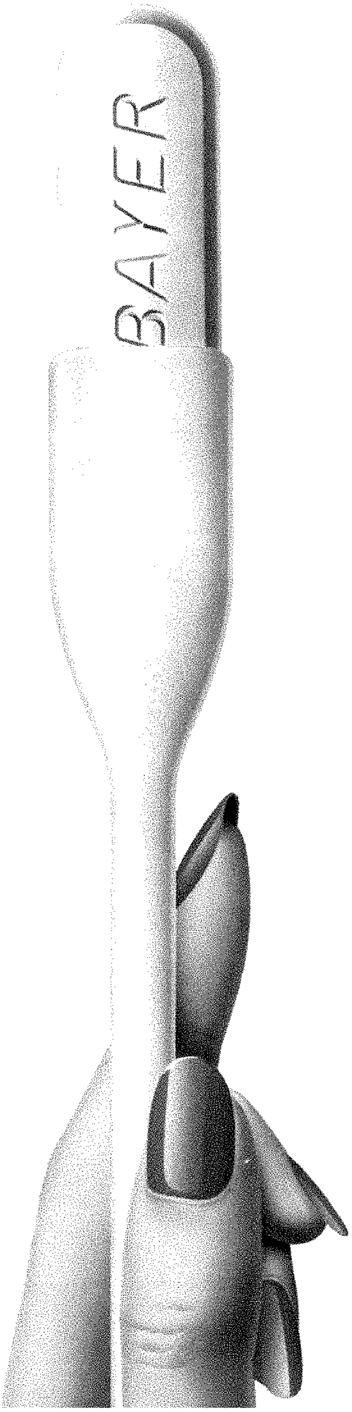

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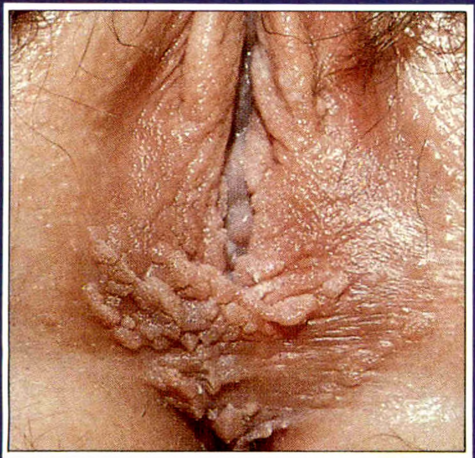

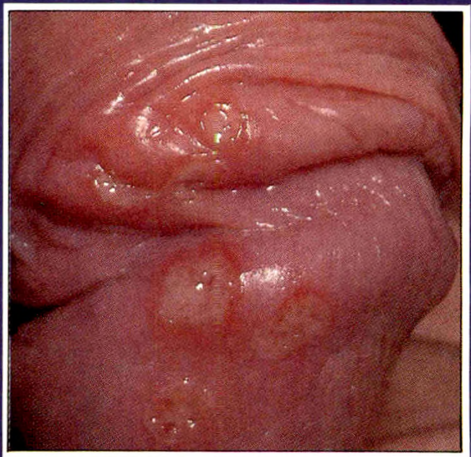

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Contra-indications, Warnings, etc.
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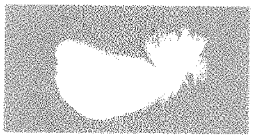

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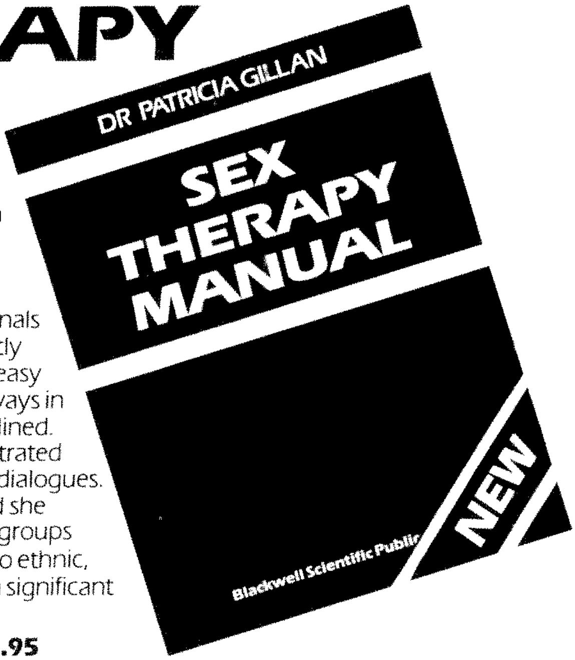

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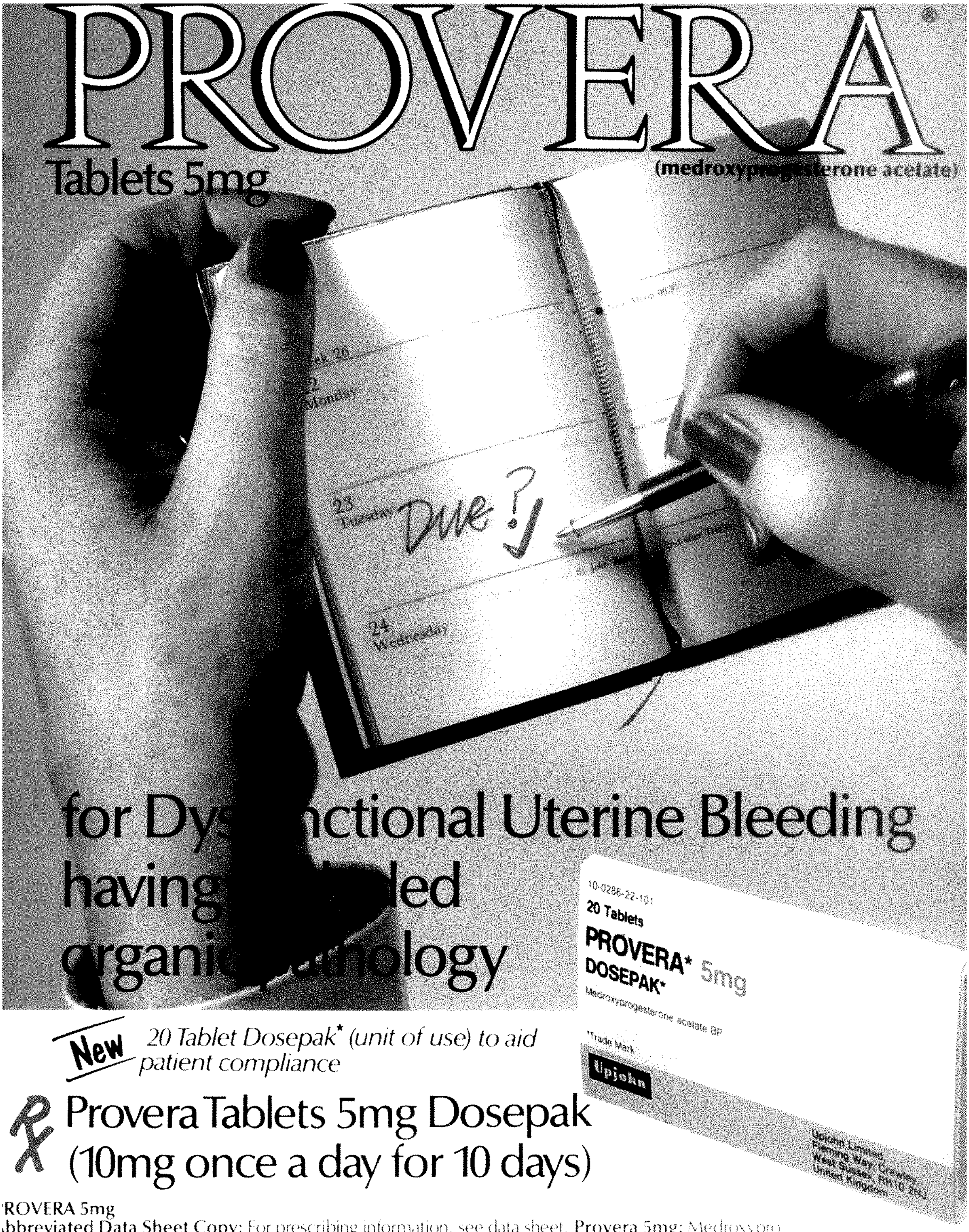
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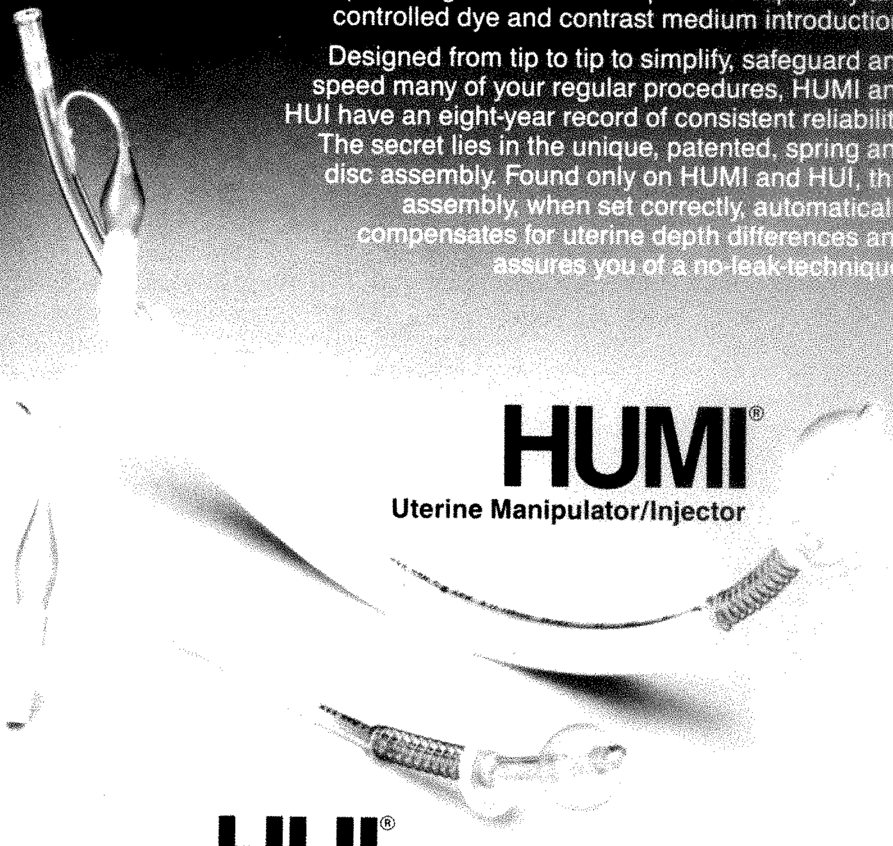

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Editors

Dr Jean Golding *Wellcome Senior Lecturer in Paediatric & Perinatal Epidemiology, Department of Child Health, Royal Hospital for Sick Children, St Michael's Hill, Bristol, UK*

Professor J.D. Baum *Department of Child Health, University of Bristol, UK*

Professor G.M. Stirrat *Department of Obstetrics and Gynaecology, University of Bristol, UK*

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COMMENTARY

Methods of treatment for cysts and abscesses of Bartholin's gland

Cysts and abscesses of Bartholin's gland, although a minor condition, cause significant pain, discomfort and disability. The condition appears most common during the reproductive years; 83% of patients are between 20 and 50 years of age (Azzan 1978).

In 1677, Caspar Bartholin, the Danish anatomist, accurately described the location of the paired greater vestibular glands which were named after him. The main function of Bartholin's gland is to keep the vestibular surface of the vulva moist by its continual secretion (Word 1966). A cyst of the gland duct develops as a result of occlusion of the duct ostium and a primary abscess of the gland is due to infection, either pyogenic or gonorrhoeal.

Many methods had been used to treat cystic enlargement of Bartholin's gland with various results. The aim of the treatment should be the preservation of the gland and its function. Resolution of the condition occurred in a high proportion, but recurrences varied according to the techniques employed. A technique that had no observed recurrences within at least 2 years could be considered most appropriate for modern treatment of Bartholin's cyst/abscess.

The earliest reported attempts were made in the 1930s. A fistula was produced using large braided silk loops, triangular metal rings and V-shaped springs inserted into the cyst through one or two stab wounds. The foreign body thus inserted caused so much discomfort that no patient allowed it to remain long enough for an epithelialized fistula to form (Davies 1948). Thus, this method of treatment was abandoned.

Davies (1948) recommended packing the cyst with gauze. The pack was changed twice weekly for 3 weeks, during which time epithelialization of the new ostium occurred. This technique required six attendances by the patient to the clinic, and was therefore time consuming for both patient and doctor. It also caused some discomfort.

A more acceptable technique which required only two attendances involved the use of an inflatable bulb-tipped catheter. This was first introduced by Krieger & Crile (1952) and modified later by Word (1964, 1966) who had used it in 60 patients without complications. After a small incision had been made, the catheter was inserted and the balloon inflated with 2–5 ml of water. The distal end of the catheter was then tucked into the vagina and the catheter was left *in situ* for 4–6 weeks during which time a fistula would epithelialize. Recurrences were uncommon with this technique which caused little discomfort (Kovar & Scott 1983). Goldburg (1970) obtained good results with this technique and reported a recurrence rate of only 13%. Kovar & Scott (1983) recommended small stab wounds. However, the technique did not enjoy wide acceptance and has been largely overlooked since.

Another method of treating Bartholin's cysts and abscesses involved aspiration with an intracath. This technique when performed under topical anaesthesia (as first line of management) allowed prompt identification of the causal organism (Cheetham 1985). It would appear that a primary Bartholin's abscess (one that is not related to an existing cyst) is commonly caused by *Neisseria gonorrhoeae* (Friedrich 1983). Aspiration of Bartholin's cysts and abscesses under topical anaesthesia (ethyl chloride) is cheap and easy to perform as an outpatient procedure and patients reported immediate relief after evacuation of the abscess's contents. Poma (1982) reported that this method of treatment showed no recurrences after 12 months. However, if there were pockets of pus, more than one puncture might be needed.

Marsupialization provides another technique for treating Bartholin's cysts and abscesses which requires only one attendance and which involves little or no discomfort. It was first described by Jacobson (1960) who reported a recurrence rate of only 2.8%. After a simple incision of the cyst, the cut edge of the lining and that of the labial skin were sutured together. Other workers (Blakey *et al.* 1966; Azzan 1978; Oliphant & Anderson 1960) have reported success rates that were less spectacular. Mathews (1966) surveyed the results obtained at the Chelsea Hospital for Women, London, for the period 1960–1966 and concluded that marsupialization was a safe method and had a low recurrence rate which could be further reduced if a Yates' drain had been used.

Up to the late 1960s a Bartholin's cyst was often treated by primary excision, and an acute abscess by incision and drainage, perhaps followed later by excision. Excision of Bartholin's duct or gland was associated with high morbidity such as haemorrhage, haematoma formation, moderate postoperative pain and later dyspareunia from considerable scarring. Now excision of Bartholin's gland is only indicated when there is suspicion of malignancy.

The carbon dioxide laser now offers an alternative means of treating Bartholin's cysts. After a simple incision, the cyst wall is vaporized from inside. The laser surgery is rapid and uncomplicated and healing occurs without scar formation (Davis 1985; Lashgari & Keene 1986). This method offers several advantages over the more conventional methods: only one treatment is usually required, a low failure rate of about 11% has been reported in the small-scale studies by Davis (1985) and Lashgari & Keene (1986), and little or no morbidity. It can be done under local anaesthesia in the outpatient clinic. The whole process takes 10–15 min and healing is complete by 2–3 weeks. There is usually no postoperative pain or infection and sexual function is not impaired. Adjacent thermal damage and tissue reaction have been shown to be minimal (Lashgari & Keene 1986). The defect created by the laser persists for a sufficient time to allow a fistula to form. The disadvantage is that the laser apparatus is expensive to install and maintain. So far only small-scale studies of this technique have been published (Davis 1985; Lashgari & Keene 1986). Further studies are needed to confirm the potential of this exciting new development in the treatment of this common and distressing condition.

J. Heah
Major RAMC
Senior Specialist in Obstetrics and Gynaecology
Louise Margaret Maternity Wing
Cambridge Military Hospital
Aldershot, Hants GU11 2AN

References

Azzan, B. B. (1978) Bartholin's cyst and abscess: a review of treatment of 53 cases. *Br J Clin Pract* **32,** 101-102

Blakey, D H., Dewhurst, C J. & Tipton, R H (1966) The long term results after marsupialization of Bartholin's cysts and abscesses *J Obstet Gynaecol Br Commonw* **73,** 1008-1009.

Cheetham, D. R. (1985) Bartholin's cyst. marsupialization or aspiration? *Am J Obstet Gynecol* **152,** 369-570

Davies, J. W. (1948) Bartholin cyst. A simple method for its restoration to function *Surg Gynecol Obstet* **86,** 329-331.

Davis, G. D. (1985) Management of Bartholin duct cysts with the carbon dioxide laser. *Obstet Gynecol* **65,** 279-280

Friedrich, E G. (1983) *Vulvar Disease,* in the series *Major Problems in Obstetrics and Gynecology.* 2nd edn, W. B Saunders, Philadelphia, pp. 68-71, 218

Goldburg, M. E. (1970) Simplified treatment for disease of Bartholin's gland. *Obstet Gynecol* **35,** 109-110

Jacobson, P (1960) Marsupialization of vulvovaginal (Bartholin) cysts: report of 140 patients with 152 cysts. *Am J Obstet Gynecol* **79,** 73-78.

Krieger, J S. & Crile, G Jr (1952) Bartholin's cyst. *Cleve Clin Q* **19,** 72-73.

Kovar, R. W. R & Scott, J. C Jr (1983) A practical, inexpensive office management of Bartholin's cyst and abscess. *Nebr Med J* **68,** 254-255.

Lashgari, M & Keene, M. (1986) Excision of Bartholin duct cysts using the CO_2 laser *Obstet Gynecol* **67,** 735-737.

Mathews, D. (1966) Marsupialization in the treatment of Bartholin's cysts and abscesses *J Obstet Gynaecol Br Commonw* **73,** 1010-1012.

Oliphant, M. M. & Anderson, G. V. (1960) Management of Bartholin duct cysts and abscesses *Obstet Gynecol* **16,** 476-478.

Poma, P A (1982) Bartholin's duct abscess: office management. *Proc Inst Med Chic* **35,** 85-86

Word, B (1964) New instrument for office treatment of cyst and abscess of Bartholin's gland. *JAMA* **190,** 777-778

Word, B. (1966) Reappraisal of Bartholin's gland *J Med Ass Alabama* **35,** 515-520.

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Genetic amniocentesis in twin pregnancies

L. PIJPERS, M. G. J. JAHODA, R. P. L. VOSTERS, M. F. NIERMEIJER,
E. S. SACHS

Summary. Eighty-three patients with twin pregnancies were seen at the University Hospital of Rotterdam between 1 January 1980 and 31 August 1985 for prenatal genetic studies. No abnormal karyotypes were found. Amniotic fluid was successfully obtained from both amniotic sacs in 77 patients. In two pregnancies elevated levels of alpha-fetoprotein (AFP) were found in both sacs. One of these pregnancies was terminated and the other continued until term. One pregnancy miscarried 4 weeks after amniocentesis at 19 weeks gestation; three women were delivered between 23 and 28 weeks, 36 at between 28 and 37 weeks and 42 women after 37 weeks. The perinatal mortality rate was 55/1000 (9 of 164). These results show that genetic amniocentesis is a safe and reliable technique in twin pregnancy but the interpretation of elevated AFP levels is complicated by the fact that AFP diffuses across the amniotic membranes between the two sacs.

The safety of genetic amniocentesis in the second trimester of pregnancy has been widely proven by several studies from large centres (Golbus *et al.* 1979; Sachs *et al.* 1982). Before 1974 a twin pregnancy was considered a contra-indication for amniocentesis; since then a small number of studies have reported different conclusions. The rate of miscarriage was found to be increased in some studies (Simpson *et al.* 1976; NICHD Study Group 1976; Palle *et al.* 1983), but not in others (Elias *et al.* 1980; Filkins & Russo 1984; Taylor *et al.* 1984). This paper presents our experience with genetic amniocentesis in 83 twin pregnancies during a period of 5·5 years.

Subjects and methods

Between January 1980 and August 1985, 83 twin pregnancies (1·2%) were observed in a total of 6960 genetic amniocenteses in our department. The indications for amniocentesis in the 83 twin pregnancies were advanced maternal age in 39 women, risk of chromosomal abnormalities in nine, risk of X-linked diseases in one, risk of neural tube defects in 32 and risk of renal abnormalities in two women.

The chromosomal analysis and the amniotic fluid alpha-fetoprotein (AFP) assay were done in the Department of Clinical Genetics in the same hospital. At the initial visit in the first trimester each patient had an obstetric and genetic assessment. Obstetric assessment included a real-time ultrasound examination to check the number of fetuses, fetal heart rate, fetal biparietal diameter (BPD) and crown–

Erasmus University, Rotterdam, The Netherlands
Department of Obstetrics and Gynaecology
L. PIJPERS
M G J JAHODA
R. P. L. VOSTERS

Department of Clinical Genetics
M F. NIERMEIJER
E S SACHS

Correspondence: L. Pijpers, MD, PhD, Department of Obstetrics and Gynaecology, Academic Hospital Rotterdam Dijkzigt, Erasmus University Rotterdam, Dr Molewaterplein 40, 3015 GD Rotterdam, The Netherlands

rump length measurements. All twins were diagnosed. Parents were given detailed information about the procedure and its possible risks and implications; they all gave informed consent to attempts at separate sampling of both amniotic sacs All amniocenteses were performed at between 112 and 143 days gestation by three experienced gynaecologists. The BPD measured 3·4 cm in all fetuses. Before amniocentesis a careful ultrasound examination included measurement of the BPD or femur length, assessment of fetal heart rate, of the presence of stomach and urinary bladder, localization of the placenta and the septum between the amniotic sacs. A suitable pool of amniotic fluid was located in each sac and the puncture sites were marked on the abdominal wall. In the case of an anterior placenta without a window, the thinnest part of the placenta was chosen to minimize damage to the fetal vessels. After disinfection and local anaesthesia of the abdominal wall, a 20 gauge 3·5 inch needle was inserted into the first amniotic cavity and 20 ml of amniotic fluid were obtained. The fluid in the first amniotic sac was then marked by injection of 1·5 ml of indigocarmine. The second puncture site was prepared similarly. When dye-stained fluid was obtained ultrasound examination was repeated and another attempt was made to obtain fluid from the second sac. In 62 patients there were two needle insertions, in eight patients three insertions and in 13 patients four insertions. Rhesus-negative women without antibodies were given 125 μg anti-D immediately after amniocentesis. To prevent labour each patient was hospitalized for 24 h complete bed-rest and ritodrine hydrochloride 10 mg was administered orally six times a day, after which the dose was reduced by 10 mg each day.

Results

In 77 of 83 (93%) twin pregnancies both amniotic sacs were successfully sampled; in the other six women the second amniotic cavity was not accessible either because it was lying behind the first cavity or because no septum was visible between the two fetuses

Chromosomal analysis of the 160 individual samples obtained revealed normal karyotypes in all cases (89 female and 71 male). Identically sexed fetuses were found in 54 pregnancies.

Elevated amniotic fluid AFP levels in both sacs were detected in two patients. The first patient had prenatal sex determination because of an increased risk of X-linked Duchenne muscular dystrophy. Two normal female karyotypes were found, but the AFP level was elevated in both sacs at 134 and 176 μg/ml, compared with normal values up to 41 μg/ml at 16 weeks gestation. This patient opted for abortion and the pregnancy was terminated with intra-amniotic prostaglandin, $PGF_{2\alpha}$. One of the aborted fetuses had microcystic structures in the renal tubules (H Rehder personal communication), while the other fetus showed no abnormalities. The second patient was referred because of ultrasonic abnormalities at 20 weeks gestation. Ultrasound examination (J. W. Wladimiroff) revealed hydronephrotic kidneys and hydro-ureters in one of the fetuses, the other being normal. Both fetal karyotypes were normal male The amniotic fluid AFP levels were elevated in both sacs at 16 and 31 μg/ml, compared with normal values up to 10 μg/ml at 20 weeks gestation. The parents decided to continue the pregnancy. At 37 weeks the patient went into labour spontaneously and because of an abnormal CTG and fetal acidosis (pH = 7·18; BE = −12) she was delivered by caesarean section of two male infants. Ultrasound examination on the first boy showed hydronephrotic kidneys and hydro-ureters, and a perfusion scan of the kidneys showed no renal function. This child died at 8 days of age because of progressive renal failure. Autopsy (J. den Hollander) showed hydronephrotic kidneys and hydro-ureters due to suburethral stenosis of the urethra. The second boy is healthy and developing well

The intra-twin differences in amniotic fluid AFP levels were compared between the known dizygotic pairs; there were no statistically significant differences in amniotic fluid AFP levels between the dizygotic twins (paired t-test, t = 0·62).

Pregnancy outcome

Follow-up of all 83 patients was obtained. Figure 1 shows the distribution of gestational age at delivery. One patient, investigated because of advanced maternal age, had a miscarriage 5 days after amniocentesis at 19 weeks gestation The two fetuses, one male and one female, showed no congenital malformations at autopsy.

Three patients were delivered between 23 and 28 weeks gestation. One of them, investigated because of advanced maternal age, was in her

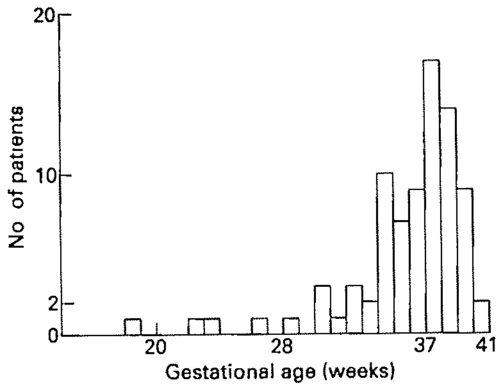

Fig. 1. Gestational age (weeks) at the time of delivery

eighth pregnancy and had had three live births. She had an incompetent cervix and despite a Shirodkar cerclage she had a preterm delivery due to chorio-amnionitis. Neither of the stillborn male babies showed any congenital malformations at autopsy. The second patient was investigated in her second pregnancy because of an increased risk of neural tube defect. Both male fetuses died *in utero* at 24 weeks gestation and neither fetus showed any congenital abnormalities at autopsy. The third patient, investigated in her third pregnancy because of an increased risk of a neural tube defect, had premature contractions and was delivered at 26 weeks. Neither of the stillborn male fetuses showed abnormalities at autopsy.

Thirty-six patients were delivered between 28 and 37 weeks and 42 patients after 37 weeks. The newborn infants weighed between 930 and 3000 g. There were three perinatal deaths among those born after 28 weeks gestation. One was a severely growth-retarded female infant born at 34 weeks who weighed 1230 g, a birthweight centile of 2·3 according to Kloosterman (1970), she had a large diaphragmatic hernia with intrathoracic displacement of the intestines. The co-twin had a birthweight of 2300 g and developed normally. The second perinatal death was a female baby born at 29 weeks gestation who weighed 1240 g and died of severe respiratory distress syndrome. The co-twin had a birthweight of 1330 g and is doing well. The third perinatal death was the baby with urethral stenosis and hydronephrosis described earlier.

In the present study, the total fetal loss within 4 weeks of the amniocentesis was 1·2% and the perinatal mortality rate was 55 per 1000 births (9 of 164). There was no relation to the number of needle insertions.

Discussion

The rate of twin pregnancy in this study is similar to the overall reported rate of about 1·2%. Twin pregnancies can be detected by ultrasound and since the introduction of real-time echography the reported detection rate of twin pregnancies before amniocentesis in the first trimester was 100% (Filkins & Russo 1984; Taylor *et al.* 1984). The success rate of obtaining amniotic fluid from both sacs was 93% in this study, similar to the results in a number of smaller series; there are only three studies with a comparable number of patients (Librach *et al.* 1984; Henry *et al.* 1984; Taylor *et al.* 1984). No chromosomal abnormalities were found in this series. All fetal karyotypes correctly corresponded to the sex of the children at birth.

In two pregnancies, amniotic fluid AFP levels were elevated in both sacs whereas only one twin showed renal abnormalities, in one pregnancy the abnormal fetus had microcystic kidneys and in the other the fetus had renal dysplasia because of urethral obstruction. There were no significant differences in amniotic fluid AFP levels between members of non-identical twin pairs in this study, which confirms the results of other studies (Librach *et al* 1984; Taylor *et al.* 1984). There have been three reports of elevated amniotic fluid AFP levels in twin pregnancy (Hunter & Cox 1979; Librach *et al.* 1984; Huber *et al.* 1984). In the first report, one twin was already dead before the amniocentesis, while the other was normal. In the second, dark-brown amniotic fluid was obtained from one sac and clear fluid from the sac of the co-twin. The fetus associated with the dark-brown fluid died subsequently at 21 weeks gestation. There are no data on any abnormalities in this fetus, the co-twin was normal. In the third pregnancy, one twin had an abnormal skull outline and an echo-free area covered by a thin membrane in the region of the abdomen, the co-twin was normal. At 30 weeks gestation one normal fetus and one fetus with multiple congenital malformations were stillborn.

AFP is known to diffuse through the amniotic membranes in spite of its high molecular weight (Franke & Estel 1978). Elevated amniotic fluid AFP levels in twin pregnancies can only be interpreted after a detailed ultrasonic study of both fetuses The risk of genetic amniocentesis in twin pregnancies varies in different studies. The estimated risk of miscarriage after genetic amniocentesis in singleton pregnancy was very low in our centre (0·7%) (Sachs *et al.* 1982). In the present study there was only one miscarriage within 4 weeks of amniocentesis which is a risk of about 1·2%. This result may have been influenced by one day of hospitalization and preventive tocolysis after the procedure. The perinatal mortality rate in this study was 55/1000 births. This is even lower than in studies on twin pregnancies without amniocentesis (Ho & Wu 1975).

References

Elias, S., Gerlie, A B., Simpson, J. L , Nadler, H. L , Sabbagha, R E. & Shkolink, A. (1980) Genetic amniocentesis in twin gestation. *Am J Obstet Gynecol* **138,** 169-174

Filkins, K., Russo, J., Brown, T., Schmerler, S & Searle, B. (1984) Genetic amniocentesis in multiple gestations. *Prenat Diagn* **4,** 223-226.

Franke, H & Estel, C. (1978) Untersuchungen uber die Ultrastrukturund Permeabilitat des Amnions unter besonderer Berucksichtigung mikrofilamentarer und mikrotubularer Strukturen *Arch Gynecol* **225,** 319-338.

Golbus, M. S., Loughman, W D., Epstein, C J , Halsbach, G., Stephens, J. & Hall, B. D. (1979) Prenatal diagnosis in 3000 amniocenteses. *N Engl J Med* **300,** 157-163

Henry, G., O'Connor, K. & Winkler, W. (1984) Low risk with amniocentesis in twin pregnancies. *Prenat Genet* **190S,** 562

Ho, S. K. & Wu, J. K. (1975) Perinatal factors and neonatal morbidity in twin pregnancy. *Am J Obstet Gynecol* **122,** 979-987.

Huber, J , Wagenbichler, P. & Bartsch, F (1984) Biamnial alpha fetoprotein concentration in twins, one with multiple malformations. *J Med Genet* **21,** 377-379.

Hunter, A. G. W. & Cox, D. M. (1979) Counselling problems when twins are discovered at genetic amniocentesis *Clin Genet* **16,** 34-42.

Kloosterman, G (1970) On intrauterine growth. The significance of prenatal care. *Int J Gynaecol Obstet* **8,** 895-904

Librach, C. L , Doran, T. A , Benzie, R J. & Jones, J. M. (1984) Genetic amniocentesis in seventy twin pregnancies. *Am J Obstet Gynecol* **148,** 585-591.

NICHD Study Group (1976) Midtrimester amniocentesis for prenatal diagnosis. *JAMA* **236,** 1471-1476

Palle, C , Andersen, J. W., Tabor, A., Lauritsen, J G , Bang, I. & Philip, J (1983) Increased risk of abortion after genetic amniocentesis in twin pregnancies *Prenat Diagn* **3,** 83-89.

Sachs, E S., Jahoda, M G. J. & Niermeijer, M. F. (1982) Prenatal diagnosis of chromosome anomalies and neural tube defects, the experience with 4600 cases In *Advances in Pathology* (Levy, E., ed.), Pergamon Press, Oxford

Simpson, N. E , Dallaire, L , Miller, J. R , Siminovitch, L., Hamerton, J L., Miller, J. & McKeen, C (1976) Prenatal diagnosis of genetic disease in Canada. Report of a collaborative study. *Can Med Assoc J* **115,** 739-746.

Taylor, M B., Anderson, R. L. & Golbus, M. S. (1984) One hundred twin pregnancies in a prenatal diagnosis program *Am J Med Genet* **18,** 419-422

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Amniotic fluid alpha-fetoprotein subfractions in fetal Trisomy 21 affected pregnancies

STEPHEN R. JONES, STUART E. EVANS, LOUISE GILLAN

Summary. The percentage contribution to the total AFP concentration in amniotic fluid from the yolk sac derived AFP was measured at 15–17 weeks gestation in 15 pregnancies affected by fetal Trisomy 21 and compared with that in 75 pregnancies with a normal outcome. The yolk sac form of AFP was reduced in parallel to the total AFP and differentiation of the subfraction from the yolk sac would offer no increase in diagnostic efficiency.

Following the observation that maternal serum alpha-fetoprotein (AFP) levels are reduced in pregnancies associated with fetal chromosomal abnormalities (Merkatz *et al.* 1984), there have been a number of reports demonstrating that AFP concentrations are reduced in the amniotic fluid surrounding fetuses with Trisomy 21 (Cuckle *et al.* 1985; Baumgarten *et al.* 1985; Voigtlander & Vogel 1985; Jones *et al.* 1986). The AFP in amniotic fluid may be separated into two forms with respect to the affinity with the lectin concanavalin-A (Ruoslahfa *et al.* 1979); the form which binds to the lectin is predominantly derived from the fetal liver, whilst the non-binding form predominantly originates from the yolk sac. The contribution to the amniotic fluid AFP from the yolk sac decreases with advancing gestational age, since the yolk sac disappears at 10–12 weeks gestation (Toftager-Larsen *et al.* 1980).

One possible explanation for the low levels of amniotic fluid AFP is that there is a reduction in the production of the protein by the fetal liver in Trisomy 21 (Cuckle *et al.* 1985). This explanation is consistent with the reduced maternal serum AFP concentration, since this AFP is believed to originate predominantly from a transplacental transfer of AFP from the fetal circulation (Wald & Cuckle 1984) (which itself derives from the fetal liver) in the absence of fetal abnormalities. The observation that serum albumin concentrations are also reduced in children and adults with Down's syndrome (Voigtlander & Vogel 1985) has been suggested as evidence to support the hypothesis of a reduced hepatic protein synthesis. However, more direct evidence comes from the finding that the concentration of AFP in cord blood of Down's syndrome infants is lower than that in matched non-trisomy controls (Cuckle & Wald 1986*a*).

The use of amniotic fluid AFP concentrations to screen for further karyotyping has been suggested and could lead to considerable reduction in costs of analysis, but, depending upon the AFP cut-offs used, a proportion of affected fetuses would be missed (Cuckle & Wald 1985, 1986*b*). To assess whether the diagnostic efficiency of this approach could be improved, the ratio of AFP not bound to concanavalin-A (Con-A non-bound AFP) to total AFP was measured (Buamah *et al.* 1981) in amniotic fluid obtained at 15–17 weeks from 15 pregnancies affected by fetal Trisomy 21 and 75 pregnancies with a normal outcome. Measurement of this ratio allows an assessment of the contribution from the yolk sac to the total amniotic fluid AFP concentration. If factors influencing both the yolk sac and the liver cause the reduction, then the ratio is expected to be similar in both affected and non-

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Department of Clinical Chemistry, Queen Elizabeth Medical Centre, Edgbaston, Birmingham
STEPHEN R. JONES
STUART E. EVANS

Department of Biochemistry, University of Birmingham
LOUISE GILLAN

Correspondence: S R. Jones

affected pregnancies. However, if liver synthesis of AFP alone is affected, then the contribution to the amniotic fluid by the yolk sac form would be expected to increase.

Subjects and methods

In all pregnancies the indication for amniocentesis was advancing maternal age (> 37 years at full term). Gestation was assessed from menstrual dates (LMP), or from ultrasound data if the LMP was in doubt. The mean age in the affected group was 39·1 years and 38·7 years in the non-affected group. The chromosomal abnormality in the affected group was regular Trisomy 21 in all cases, and confirmed by karyotyping. No abnormalities in the control group were reported to the regional amniocentesis audit programme. Samples were stored frozen for up to 2·5 years, and the length of storage of samples was matched in the two groups.

The percentage Con-A non-bound AFP was measured as described by Buamah *et al.* (1981) using an in-house radioimmunoassay, which performed satisfactorily on an external quality assessment programme. Pooled amniotic fluids over the range of interest were used as controls and gave between-batch variation of 9–11%. No effort was made to decrease this imprecision. Blood-stained samples were not included in this study.

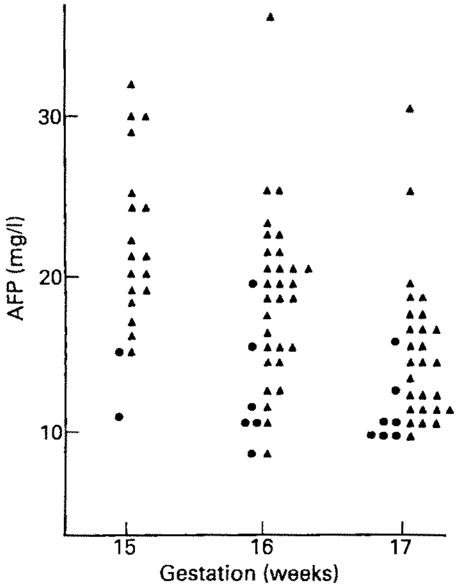

Fig. 1. Comparison of the AFP concentration in amniotic fluid from affected (●) and non-affected (▲) pregnancies at 15–17 weeks gestation.

Results

The concentration of the total AFP in the control and affected pregnancies at each gestation is shown in Fig. 1. As expected from previous studies the mean (SD) of the total AFP values (expressed as multiples of the median) was higher in the samples from the control subjects than in those from the pregnancies affected by Trisomy 21 [1·05 (0·30) compared with 0·76 (0·19); $P<0·01$]. However, since there is no correlation between the percentage Con-A non-bound AFP and total AFP concentration in pregnancies with a normal outcome (Toftager-Larsen *et al.* 1980), there would be no advantage in further matching samples for total AFP concentration.

The percentage of Con-A non-bound AFP at each gestation in the two groups is shown in Fig. 2. The results in the control group are consistent with other reported series (Toftager-Larsen *et al.* 1980; Buamah *et al.* 1981). It can be seen that there is no consistent difference between the ratios of Con-A non-bound AFP to total AFP in the two groups. There is a progressive decline in the contribution by Con-A non-bound AFP with gestational age (Toftager-Larsen *et al.* 1980). After correcting for gestational age variations using analysis of covariance, there was no significant difference between the affected and non-affected groups. (Gestational age adjusted means of 18·8% (SD 4·4) and 16·1% (SD 4·4) in normal and Trisomy 21 affected pregnancies; $P \sim 0·07$.)

Discussion

Amniotic fluid AFP may be separated into two forms by concanavalin-A. These forms are predominantly derived from the fetal liver and the fetal yolk sac. In fetal blood at 15–17 weeks gestation, the AFP is mainly of the liver type (Cuckle & Wald 1986*b*), and subsequently when there is a defect leading to transfer of the AFP-rich fetal blood-derived proteins into the amniotic fluid (e.g. neural tube defect, exomphthalos), then the percentage contribution of the fetal yolk sac form decreases due to increased concentration of the liver form. This was proposed as an additional test to help verify fetal abnormalities before the acetyl cholinesterase isoenzyme testing

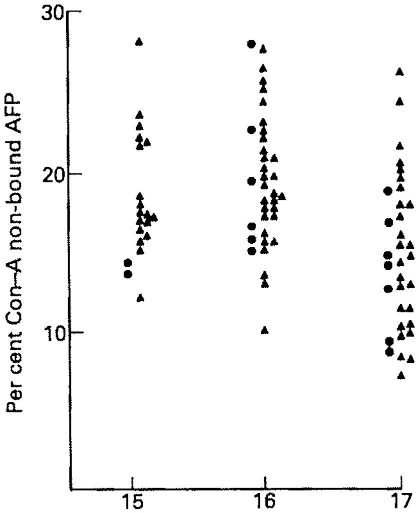

Fig. 2. Percentage contribution to the total AFP of the Con-A non-bound fraction in affected (●) and non-affected (▲) pregnancies.

It has been suggested that maternal blood AFP is derived from the transplacental transfer of AFP in normal pregnancies (contribution from the transfer via the amnion is estimated to be 15% in these cases) (Wald & Cuckle 1984). Hence a low maternal serum AFP in trisomy-affected pregnancies might reflect a poor fetal hepatic production of AFP at these gestations (Cuckle *et al.* 1985), and additional evidence for this hypothesis comes from the observations that there is significantly lower AFP concentration in babies with Trisomy 21.

The contribution of the yolk sac form of AFP to the total AFP was investigated since, if the reduction of AFP in the amniotic fluid was due to a reduced liver production alone in Trisomy 21, then the percentage contribution from the yolk sac would be greater in these cases. Assuming an average reduction of 30% in the AFP concentration, then the mean percentage contribution from the yolk sac would increase from 20 to 28%, 20 to 29% and 15 to 21% at 15, 16 and 17 weeks respectively. This clearly is not the case. The differences between the affected and non-affected cases did not reach significance (*P*>0·05), and the percentage contribution from the yolk sac form was slightly lower rather than higher than that for the unaffected pregnancies.

If the cause of a low maternal serum and amniotic fluid AFP values in a fetus affected by Trisomy 21 is a reduced production of the protein by the liver, then the production of the protein by the yolk sac form must be reduced to a similar extent. Since it has been suggested that an AFP level less than the 5th centile (Cuckle & Wald 1986*b*) could be used to select amniotic fluids for karyotyping from patients at low risk of chromosomal defects; this work demonstrates there will be no further advantage in looking at the AFP subfractions discussed here to improve this type of approach.

References

Baumgarten, A., Schoenfeld, M , Mahoney, M J , Greenstein, R M & Saal, H. M. (1985) Prospective screening for Down syndrome using maternal serum AFP. *Lancet* **i**, 1281-1282.

Buamah, P. K., Taylor, P. & Milford-Ward, A. (1981) Concanavalin A binding of alphafetoprotein in amniotic fluid as an aid to the diagnosis of neural tube defects *Clin Chem* **27**, 1658-1660

Cuckle, H. S., Wald, N J., Lindenbaum, R. H. & Jonasson, J. (1985) Amniotic fluid AFP levels and Down syndrome *Lancet* **i**, 290-291

Cuckle, H. S & Wald, N. J. (1986*a*) Cord serum alphafetoprotein and Down's syndrome. *Br J Obstet Gynaecol* **93**, 408-416

Cuckle, H S. & Wald, N. J (1986*b*) Amniotic fluid alpha-fetoprotein levels in Down syndrome. *Lancet* **ii**, 290-291.

Jones, S. R., Evans, S E., Bowser-Riley, S. M , Holten, M. A., Leedham, P & McMahon, G (1986) Amniotic fluid alpha-fetoprotein levels and Trisomy 21. *Lancet* **i**, 1507-1508

Merkatz, I. R., Nitowsky, H. M., Macri, J. N. & Johnson, W. E (1984) An association between low maternal serum alphafetoprotein and fetal chromosomal abnormalities. *Am J Obstet Gynecol* **148**, 886-892.

Ruoslahfa, E., Pekkala, A. & Comings, D E. (1979) Determination of subfractions of amniotic fluid alphafetoprotein in diagnosis of spina bifida and congenital nephrosis *Br Med J* **ii**, 768.

Toftager-Larsen, K., Kjaersgaard, E., Jacobsen, J Chr. & Norgaard-Pedersen, B. (1980) Reactivity of amniotic fluid alphafetoprotein with concanavalin A in relation to gestational age: clinical implications. *Clin Chem* **26**, 1656-1659.

Voigtlander, T. & Vogel, F (1985) Low alpha-fetoprotein and serum albumin levels in Morbus Down may point to a common regulatory mechanism *Hum Genet* **71**, 276-277.

Wald, N J. & Cuckle, H. S (1984) Open neural tube defects In *Antenatal and Neonatal Screening* (Wald, N. J., ed.), Oxford University Press, Oxford, pp. 25–73.

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Low second trimester maternal serum unconjugated oestriol in pregnancies with Down's syndrome

J. A. CANICK, G. J. KNIGHT, G. E. PALOMAKI, J. E. HADDOW,
H. S. CUCKLE, N. J. WALD

Summary. Second trimester maternal serum unconjugated oestriol levels were measured in the stored serum samples from 22 pregnancies associated with Down's syndrome and 110 unaffected control pregnancies, matched for maternal age, gestational age, duration of storage of the serum sample, smoking habits and maternal weight. The serum unconjugated oestriol level of each affected pregnancy was expressed as a multiple of the median (MoM) of its five matched controls. The unconjugated oestriol levels were significantly lower in the affected pregnancies than in the unaffected pregnancies; the median MoM was 0·79 ($P<0{\cdot}05$). This association between low serum unconjugated oestriol and fetal Down's syndrome early in pregnancy raises the possibility that serum unconjugated oestriol measurement may be added to maternal age and alpha-fetoprotein measurement in the antenatal screening for Down's syndrome.

Low maternal serum and amniotic fluid alpha-fetoprotein (AFP) are both associated with Down's syndrome pregnancies (Merkatz *et al.* 1984; Cuckle *et al.* 1984, 1985; Anonymous 1984). AFP concentration is, on average, even lower in cord sera from fetuses with Down's syndrome, leading to the suggestion that synthesis and/or secretion of AFP by the fetal liver is reduced (Cuckle *et al.* 1986). This raised the possibility that the secretion of other fetal liver products might also be reduced in association with Down's syndrome and prompted us to investigate whether this was the case with unconjugated oestriol, a steroid product of the feto-placental unit requiring the participation of the fetal liver for its synthesis (Siiteri & MacDonald 1966). This possibility was reinforced by the report from Jorgensen & Trolle (1972) that total urinary oestriol excretion in the third trimester was lower in Down's syndrome pregnancies than in unaffected pregnancies.

Methods

We identified 22 pregnancies associated with Down's syndrome in a group of women who had serum AFP estimations for screening in Maine and in Rhode Island between late 1983 and mid-1985 and from whom second trimester maternal serum samples were stored at −20°C. Two of these were identified as a result of low maternal

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Department of Pathology and Laboratory Medicine, Brown University Women and Infant's Hospital, Providence, Rhode Island, USA
J. A. CANICK *Associate Professor*

Foundation for Blood Research, Scarborough, Maine, USA
G. J KNIGHT *Director, Radioimmunoassay Laboratory*
G. E. PALOMAKI *Biostatistician*
J. E. HADDOW *Associate Medical Director*

Department of Environmental and Preventive Medicine, St Bartholomew's Hospital Medical College, London EC1M 6BQ, UK
H S. CUCKLE *CRC Senior Lecturer*
N. J. WALD *Professor and Head of Department*

Correspondence: Dr J. A. Canick

serum AFP measurements, four were identified after amniocentesis for advanced maternal age, and 16 were identified after birth from karyotype records. Each Down's syndrome sample was matched with five control samples from unaffected pregnancies matched for gestation (completed weeks), smoking habits, maternal weight (within 20 pounds), length of freezer storage of samples (within 2 months) and maternal age (within 3 years). All samples were retrieved from storage and thawed just before being assayed at the Women and Infants Hospital, Rhode Island, without knowledge of whether they were from affected or unaffected pregnancies.

Unconjugated oestriol was measured using a direct, non-extraction, radioimmunoassay (AMERLEX Oestriol RIA Kit, Amersham International). The assay was modified by doubling the sample volume to 40 µl for the standards, controls, and patients to increase sensitivity to allow detection of unconjugated oestriol levels found in the second trimester. This modification produced a standard curve ranging from 1·4 to 52·0 nmol/l with a sensitivity of 1·0 nmol/l. The between-assay coefficients of variation for the 4·5 and 11·8 nmol/l controls were 11·6% and 5·7% respectively. For study samples, each affected pregnancy and its associated controls were analysed in the same run to avoid between-assay variability.

Results

Table 1 shows the serum concentrations of unconjugated oestriol for each affected pregnancy and the five matched unaffected pregnancies. The value for the affected pregnancy is also expressed as a multiple of the median (MoM) value of the five matched unaffected pregnancies. Of the 22 affected pregnancies 16 (73%) had MoM values <1·0. The median unconjugated oestriol MoM for the Down's syndrome pregnancies was 0·79, a statistically significant reduction (χ^2_1 = 4·0, *P*<0·05, by analysis of vari-

Table 1. Maternal serum unconjugated oestriol in 22 pregnancies associated with Down's syndrome and matched controls

		Unconjugated oestriol concentration (nmol/l)						Down's syndrome unconjugated oestriol value divided by median of five matched controls (MoM)
Number	Completed weeks gestation	Down's syndrome pregnancies	Matched controls* (1)	(2)	(3)	(4)	(5)	
1	15	2·70	1·94	3·36	6·41	8·84	10·16	0·42
2	17	3·12	3·40	4·96	5·27	7·59	9·67	0·59
3	20	6·87	7·18	10·19	11·06	11·41	16·37	0 62
4	15	2·08	1·11	1·91	3·29	3·68	4·20	0·63
5	16	2·70	2·77	4·16	4·23	6·41	6·59	0·64
6	18	5·83	6·97	8·81	9·05	10·12	12·76	0·64
7	16	3·64	3·33	4·33	5·41	5·96	6·43	0·68
8	16	3·68	3·40	4·54	5·44	7·21	7·32	0·62
9	17	5·41	6·55	6·97	7·52	7·77	8·29	0 72
10	20	6·48	5·10	7·00	8·67	9·53	10·37	0·75
11	17	5·06	4·89	5·17	6·73	7·11	7·70	0·75
12	17	4·26	4·54	5·10	5·10	10·23	12·76	0·84
13	16	4·65	3·81	4·09	5·48	6·35	7·56	0·85
14	15	3·16	2·50	2·60	3·68	6·41	7·25	0·86
15	17	4·33	3·88	4·30	4·68	5·13	5·27	0·93
16	19	8·25	7·77	7·94	8·70	12·00	29·72	0·95
17	16	5·10	4·20	4·85	5·06	5·79	8·11	1·01
18	17	6·17	3·50	4·92	5·93	7·63	7·73	1·04
19	16	5·10	4·20	4·79	4·82	4·92	5·27	1·06
20	15	5·06	2·98	3·30	4·33	4·96	4·96	1·17
21	16	5·83	4·20	4·44	4·65	5·31	6·69	1·25
22	17	7·14	4·85	4·85	5·10	5·34	7·11	1·40
							Median	0·79

*Unconjugated oestriol results shown in ascending rank order ance of the ranks of values within each matched set).

Discussion

Our results show that maternal serum unconjugated oestriol levels in the second trimester are significantly lower in pregnancies associated with Down's syndrome than in control pregnancies. We matched Down's syndrome pregnancies and control pregnancies for five factors, two of which show an important association with unconjugated oestriol levels (gestational age and smoking). This was suggested by previous work (De Hertogh *et al.* 1975; Tulchinsky & Abraham 1971; Mochizuki *et al.* 1984) and additional data that we had collected indicating that maternal serum unconjugated oestriol levels increased in a log-linear fashion by about 20% per week from 15 to 20 weeks gestation and were about 15% lower in smokers than in non-smokers. Duration of storage and maternal weight had only a small effect on the concentration of serum unconjugated oestriol, while maternal age had no discernible effect.

The explanation for the decreased serum unconjugated oestriol levels in pregnancies associated with Down's syndrome is unknown. The synthesis of unconjugated oestriol is dependent on the fetal adrenal cortex, the fetal liver and the placenta. Immaturity of any or all of these organs in fetuses with Down's syndrome could account for the low unconjugated oestriol levels. There are data that lend some support to this explanation. Down's syndrome fetuses are immature as evidenced by their low average birthweight and placental weight (Butler & Alberman 1969; Heinonen *et al.* 1977) both of which are, in turn, associated with low maternal serum unconjugated oestriol levels in the third trimester of pregnancy (Heap 1972; Perry *et al.* 1986). Evidence suggesting organ-specific involvement arises from observation by Bech & Tygsrup (1972) that the fetal zone of the adrenal cortex of three out of eight Down's syndrome infants was hypoplastic and that the fetal serum AFP levels in Down's syndrome pregnancies are low (Cuckle *et al.* 1986)—the liver being a shared site of synthesis for both AFP and the oestriol precursor 16-alpha-hydroxydehydroepiandrosterone sulphate. Although fetal immaturity is a plausible explanation for the low serum unconjugated oestriol levels in Down's syndrome pregnancies, it remains a speculation.

The association between low maternal serum unconjugated oestriol and Down's syndrome holds out the prospect that serum unconjugated oestriol measurement may be added to maternal age determination and maternal serum AFP measurement in the antenatal screening for Down's syndrome. First, however, more extensive data are needed to assess the magnitude of the association, its sensitivity and specificity, and the extent to which it is independent of AFP (Wald *et al.* 1988).

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References

Anonymous (1985) Low maternal serum alpha-fetoprotein and Down syndrome. *Lancet* **i**, 259-260.

Bech, K. & Tygstrup, L. (1972) Down's syndrome and oestriol excretion in late pregnancy. *Lancet* **ii**, 1261.

Butler, N R. & Alberman, E D. (eds) (1969) *Perinatal Problems. The Second Report of the 1958 British Perinatal Mortality Survey.* E. Edinburgh & S. Livingstone Ltd.

Cuckle, H. S., Wald, N. J. & Lindenbaum, R. H. (1984) Maternal serum alpha-fetoprotein measurement: a screening test for Down syndrome. *Lancet* **i**, 926-929

Cuckle, H. S., Wald, N. J., Lindenbaum, R H. & Jonasson, J. (1985) Amniotic fluid AFP levels and Down syndrome. *Lancet* **i**, 290-291.

Cuckle, H. S , Wald, N. J. & Lindenbaum, R H (1986) Cord serum alpha-fetoprotein and Down's syndrome. *Br J Obstet Gynaecol* **93**, 408-410.

De Hertogh, R., Thomas, K., Bietlot, Y., Vanderheyden, I. & Ferin, J. (1975) Plasma levels of unconjugated estrone, estradiol and estriol and of HCS throughout pregnancy in normal women. *J Clin Endocrinol Metab* **40**, 93-101.

Heap, R. B. (1972) Role of hormones in pregnancy. In *Reproduction in Mammals, Book 3: Hormones in Reproduction* (Austin, C. R. & Short, R. V., eds), Cambridge Press, pp. 73-105.

Heinonen, O. P., Slone, D. & Shapiro, S. (1977) *Birth Defects and Drugs in Pregnancy.* Littleton, Publishing Sciences Group, Massachusetts.

Jørgensen, P. I. & Trolle, D. (1972) Low urinary oestriol excretion during pregnancy in women giving birth to infants with Down's syndrome. *Lancet* **ii**, 782-784.

Merkatz, I. R., Nitowsky, H. M., Macri, J. N. & Johnson, W. E. (1984) An association between low maternal serum alpha-fetoprotein and fetal chromosomal abnormalities *Am J Obstet Gynecol* **148,** 886-894.

Mochizuki, M., Mruo, T., Masuko, K. & Ohtsu, T (1984) Effects of smoking on fetoplacental-maternal system during pregnancy. *Am J Obstet Gynecol* **149,** 413-420

Perry, L., Hickson, R., Obiekwe, B. C & Chard, T (1986) Maternal oestriol levels reflect placental function rather than foetal function *Acta Endocrinol* **111,** 563-566.

Siiteri, P K. & MacDonald, P. C. (1966) Placental estrogen biosynthesis during human pregnancy *J Clin Endocrinol Metab* **26,** 751-761.

Tulchinksy, D. & Abraham, G. E (1971) Radioimmunoassay of plasma estriol. *J Clin Endocrinol Metab* **33,** 775-782

Wald, N. J , Cuckle, H. S., Densem, J W., Nanchahal, K , Canick, J. A , Haddow, J E., Knight, G. J & Palomaki, G E. (1988) Maternal serum unconjugated oestriol as an antenatal screening test for Down's syndrome *Br J Obstet Gynaecol* **95,** 334-341

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Maternal serum unconjugated oestriol as an antenatal screening test for Down's syndrome

N. J. WALD, H. S. CUCKLE, J. W. DENSEM, K. NANCHAHAL,
J. A. CANICK, J. E. HADDOW, G. J. KNIGHT, G. E. PALOMAKI

Summary. The median maternal serum unconjugated oestriol level between 13 and 27 weeks gestation in 77 pregnancies associated with Down's syndrome was lower than the median level in 385 unaffected control pregnancies matched for maternal age, gestational age, and duration of serum sample storage ($P<0{\cdot}001$). The median level for the affected pregnancies was 73% of that in the controls. Low unconjugated oestriol levels can be used to detect fetal Down's syndrome; at cut-off levels selected to detect at least 35% of affected pregnancies, unconjugated serum oestriol was a better screening test than either maternal age or serum alpha-fetoprotein (AFP). The use of all three variables in combination to select women with a 1:250 or greater risk of a Down's syndrome term pregnancy would yield a 45% detection rate with a false-positive rate of 5·2%. The same detection rate using maternal age alone or using age and serum AFP in combination would yield higher false-positive rates, 15% and 9·8% respectively. The addition of unconjugated oestriol to a Down's syndrome screening programme would therefore be more efficient than the use of age and AFP alone; for a given detection rate fewer women would need an amniocentesis or, for a given percentage of women having an amniocentesis, more pregnancies with Down's syndrome would be detected.

Our observation that maternal serum unconjugated oestriol levels were significantly lower in pregnancies associated with Down's syndrome than in unaffected pregnancies of the same gestational age (Canick *et al.* 1988) prompted us to investigate the association further. Using a bank of mid-trimester antenatal serum samples we designed a study to investigate whether serum unconjugated oestriol measurement would be a useful antenatal screening test for Down's syndrome and, if so, how it might be used in conjunction with the determination of maternal age and maternal serum alpha-fetoprotein (AFP).

Methods

General

A −40°C antenatal serum bank was used relating to pregnancies from women attending for

Department of Environmental and Preventive Medicine, St Bartholomew's Hospital Medical College, London EC1M 6BQ, UK
N. J. WALD *Professor and Head of Department*
H. S. CUCKLE *CRC Senior Lecturer*
J. W. DENSEM *Computer Manager*
K. NANCHAHAL *Computer Programmer*
Department of Pathology and Laboratory Medicine, Brown University Women and Infant's Hospital, Providence, Rhode Island, USA
J. A CANICK *Associate Professor*
Foundation for Blood Research, Scarborough, Maine, USA
J. E. HADDOW *Associate Medical Director*
G. J. KNIGHT *Director, Radioimmunoassay Laboratory*
G. E. PALOMAKI *Biostatistician*
Correspondence: N. J. Wald, Department of Environmental and Preventive Medicine, St Bartholomew's Hospital Medical College, Charterhouse Square, London EC1M 6BQ

antenatal care at the John Radcliffe Maternity Hospital, Oxford, between 1973 and 1983. Seventy-seven antenatal serum samples were identified from 77 singleton pregnancies associated with Down's syndrome (cases). (The extra nine cases compared to our previously reported series of 68 (Cuckle *et al.* 1987) represent pregnancies from which serum had been collected and stored but which had not undergone AFP screening.) Each sample was matched with five stored control samples from unaffected pregnancies matched for maternal age (within the same year), gestational age (usually within 1 week) and duration of storage (within 1 year) of the sample. The samples were retrieved from storage and assayed for unconjugated oestriol and AFP. None of the cases or controls were from pregnancies associated with a neural-tube defect, and all the samples were collected between 13 and 27 completed weeks gestation. The affected pregnancies were identified from the same sources as described previously (Cuckle *et al.* 1984) namely (i) the records of the Department of Medical Genetics, Churchill Hospital, Oxford, (ii) the delivery records at the John Radcliffe Maternity Hospital, Oxford, (iii) notification of congenital malformations made at the Office of Population Censuses and Surveys, (iv) the Oxford obstetric data system for infants born at the John Radcliffe, (v) records held by the local hospital for handicapped children (Park Hospital) and (vi) the handicapped egister for Oxfordshire.

Unconjugated oestriol was assayed using a lirect, non-extraction radioimmunoassay Amerlex oestriol RIA kit, Amersham). As efore (Canick *et al.* 1988), the assay was modiied by doubling the sample volume to 40μl for ll specimens analysed. Maternal serum AFP vas assayed using an immunoradiometric assay Boots-Celltech Diagnostics Ltd). All the assays vere performed within 1 month. Cases and conrols were always assayed in the same analytical atch, and the assays were done without knowedge of whether the samples were from affected r unaffected pregnancies.

Unconjugated oestriol levels were expressed n units of mass concentration and in multiples of he median for unaffected pregnancies of the ame gestational age (MoM) using a linear egression of unaffected medians on gestational ge weighted for the number of women tested at ach week of gestation. AFP levels were also expressed in MoM but a log linear regression was used.

Method of estimating detection rates and false-positive rates from our results

For each screening variable (maternal age, unconjugated oestriol and AFP) considered alone and in combination, we estimated the false-positive rate (proportion of unaffected pregnancies regarded as positive) corresponding to a specified detection rate (proportion of affected pregnancies regarded as positive).

(i) For maternal age alone these rates were derived from the age distributions of affected and unaffected pregnancies. The age distribution for Down's syndrome was estimated by applying the risk of Down's syndrome for specific years and days of age to the age distribution in years of maternities in England and Wales between 1981 and 1985 after dividing the number each year by 365. The risk for specific years and days of age was estimated as described previously (Cuckle *et al.* 1987). The age distribution for unaffected pregnancies was obtained by subtraction.

(ii) For AFP alone the detection and false-positive rates were derived from areas under the Gaussian frequency distributions of log AFP previously defined (Cuckle *et al.* 1987).

(iii) For unconjugated oestriol alone we first confirmed that the data fitted Gaussian frequency distributions satisfactorily (see Results). Since the assays were performed under research conditions within 1 month, an estimate of long-term between-batch assay variance was added to the observed variances of unconjugated oestriol in order to obtain estimates of the standard deviations that would be found in routine practice. The detection and false-positive rates were then estimated from Gaussian distributions with the adjusted parameters. The long-term between-batch assay variance was estimated to be 0·0034. This was obtained by the repeated assay of two serum samples in many batches: (a) a serum sample with mean unconjugated oestriol concentration of 1·39 MoM at 17 weeks gestation assayed 58 times over an 8-month period and (b) a serum sample with mean concentration of 0·50 MoM at 17 weeks gestation assayed 47 times over a 7-month period.

(iv) For combinations of variables detection and false-positive rates were estimated using the method described previously (Cuckle *et al.* 1987) in which each woman's risk of a Down's syndrome birth is estimated from the combined variables and regarded as positive if it is greater than or equal to a risk cut-off level. The only modification was that the fitted Gaussian frequency distributions were used rather than the observed distributions. For combinations of all three variables we first confirmed that the unconjugated oestriol and log AFP levels fitted a bivariate Gaussian frequency distribution (see Results).

Results

Maternal serum unconjugated oestriol

Figure 1 shows the individual unconjugated oestriol level for each pregnancy associated with Down's syndrome together with the median and the 25th and 75th centile values for unaffected pregnancies, based on linear regressions of unconjugated oestriol on gestational age weighted for the number of women tested in each week of gestation. The observed medians for unaffected pregnancies at each week of gestation are also shown. On average, the unconjugated oestriol values were significantly lower for the Down's syndrome pregnancies than for the unaffected pregnancies ($P<0{\cdot}001$, by analysis of variance of the ranks within matched sets). There was no tendency for the difference to be materially different in any particular week from 13 to 27 weeks gestation.

Table 1 shows the 25th, 50th and 75th centiles of maternal serum unconjugated oestriol expressed in MoM for the Down's syndrome and unaffected pregnancies. The median for affected pregnancies was only 73% of the value for unaffected pregnancies ($P<0{\cdot}001$).

Table 2 shows the distribution of maternal serum unconjugated oestriol MoM values in Down's syndrome and unaffected pregnancies and Fig. 2 is a probability plot showing a comparison of the observed values with those obtained from Gaussian frequency distributions represented as straight lines. The figure shows that the Gaussian distributions fitted the data well between 0·40 and 1·40 MoM. The mean and standard deviation for the Gaussian distributions for affected and unaffected pregnancies (0·73, 0·25 and 1·00, 0·26 MoM respectively) were estimated from the medians and 10th–90th centile ranges. The Gaussian distributions with standard deviations adjusted to allow for long-term assay imprecision (0·26 and 0·27 MoM) are shown in Fig. 3.

Table 3 shows the median maternal serum unconjugated oestriol MoM values in Down's syndrome and unaffected pregnancies according to maternal age. In both affected and unaffected

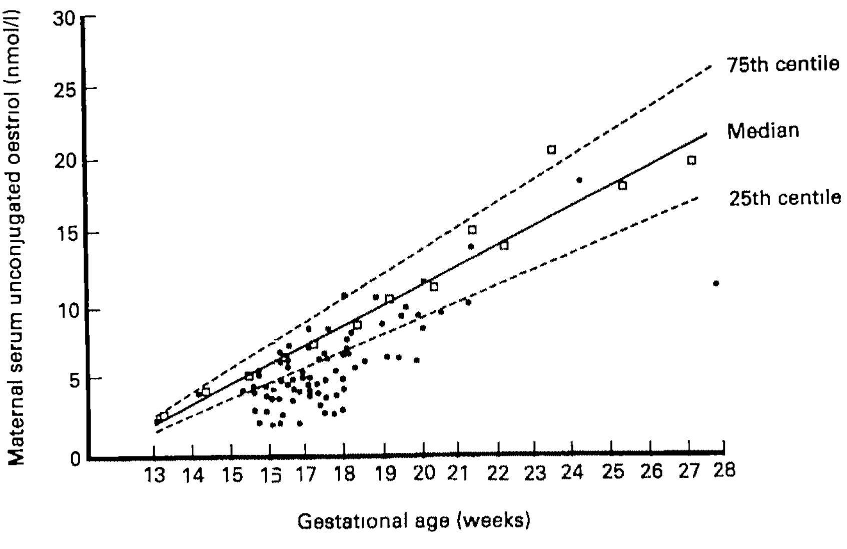

Fig. 1. Maternal serum unconjugated oestriol levels in 77 pregnancies with Down's syndrome (●) in relation to the median, 25th, and 75th centile level for 385 unaffected pregnancies obtained by weighted linear regression on gestational age (The observed unaffected medians for each week of gestation from 13 to 27 weeks are also shown (□) based on 7, 3, 20, 122, 113, 50, 29, 19, 11, 1, 2, 0, 3, 0, 5 pregnancies respectively.)

Table 1. Twenty-fifth, 50th (median) and 75th centile of maternal serum unconjugated oestriol in Down's syndrome pregnancies and unaffected pregnancies

	Unconjugated oestriol level (MoM)	
Centile	Down's syndrome pregnancies ($n=77$)	Unaffected pregnancies ($n=385$)
25th	0·59	0·83
50th (median)	0·73	1·00
75th	0·90	1·19

MoM, Multiple of the median for unaffected pregnancies of the same gestational age.

Table 2. Proportion of the 77 Down's syndrome pregnancies and the 385 unaffected pregnancies with maternal serum unconjugated oestriol levels less than or equal to specified cut-off levels

Unconjugated oestriol level (MoM)	Down's syndrome pregnancies (%)	Unaffected pregnancies (%)
≤0·40	9·1	1·3
≤0·50	16	3·1
≤0·60	26	4·9
≤0·70	46	9·6
≤0·80	62	21
≤0·90	75	35
≤1·00	86	50

MoM, Multiple of the median for unaffected pregnancies of the same gestational age.

pregnancies the median level was similar at each maternal age, indicating that maternal serum unconjugated oestriol provides a measure of the risk of Down's syndrome that is independent of maternal age.

Maternal serum unconjugated oestriol and alpha-fetoprotein

Table 4 shows that in both Down's syndrome and unaffected pregnancies the median maternal serum unconjugated oestriol MoM value increases with increasing maternal serum AFP level. The correlation between unconjugated oestriol and log AFP levels is statistically significant ($r=0{\cdot}21$, $P<0{\cdot}05$ for Down's syndrome pregnancies and $r=0{\cdot}20$, $P<0{\cdot}001$ for unaffected pregnancies). A bivariate Gaussian frequency distribution fitted the data reasonably well (see Appendix I). Logistic regression analysis demonstrated that unconjugated oestriol was a stronger predictor of the risk of Down's syndrome than AFP, though each provided additional information that was statistically significant ($\chi^2_1=45{\cdot}4$, $P<0{\cdot}0001$ for unconjugated oestriol added to AFP; $\chi^2_1=11{\cdot}2$, $P<0{\cdot}001$ for AFP added to unconjugated oestriol).

Table 5 shows the estimated false-positive rate according to specified Down's syndrome detection rates for maternal age, serum unconjugated oestriol and AFP. At low levels of detection (at or below 35%) maternal age alone is a better screening variable than either of the other two alone but at higher levels of detection unconjugated oestriol is the better. Table 5 also shows the extent to which the combination of maternal age, AFP and unconjugated oestriol is better than any one variable alone or age and either of the other two variables in combination.

Discussion

We have already noted that the explanation for the low maternal serum unconjugated oestriol levels in Down's syndrome pregnancies is unknown but may be due to the immaturity of fetuses with Down's syndrome (Canick *et al.* 1988). In normal pregnancy, the fetal adrenal cortex produces dehydroepiandrosterone sulphate (DHEAS) which enters the fetal circulation and passes to the fetal liver, where most of it undergoes 16-alpha-hydroxylation. The newly formed 16-alpha-hydroxy-DHEAS reaches the placenta, where it is converted in four enzymatic steps (sulphatase, 3-beta-hydroxysteroid dehydrogenase-4,5-isomerase, aromatase and 17beta-hydroxysteroid dehydrogenase) to oestriol. Oestriol then diffuses into the maternal compartment, where it can be measured as an unconjugated steroid, its rise in concentration paralleling the growth of the fetus and placenta. Unlike total oestriol, unconjugated oestriol in maternal serum is almost entirely derived from the fetus and the placenta (Siiteri & MacDonald 1966). For this reason it was chosen as a more sensitive indicator of altered fetal metabolism than total serum oestriol.

Our results show that maternal serum unconjugated oestriol levels in pregnancies with and without Down's syndrome are sufficiently different for unconjugated oestriol measurement to be a useful screening test for Down's syndrome. Unconjugated oestriol is a screening variable that is independent of maternal age and largely independent of AFP—hence the use of

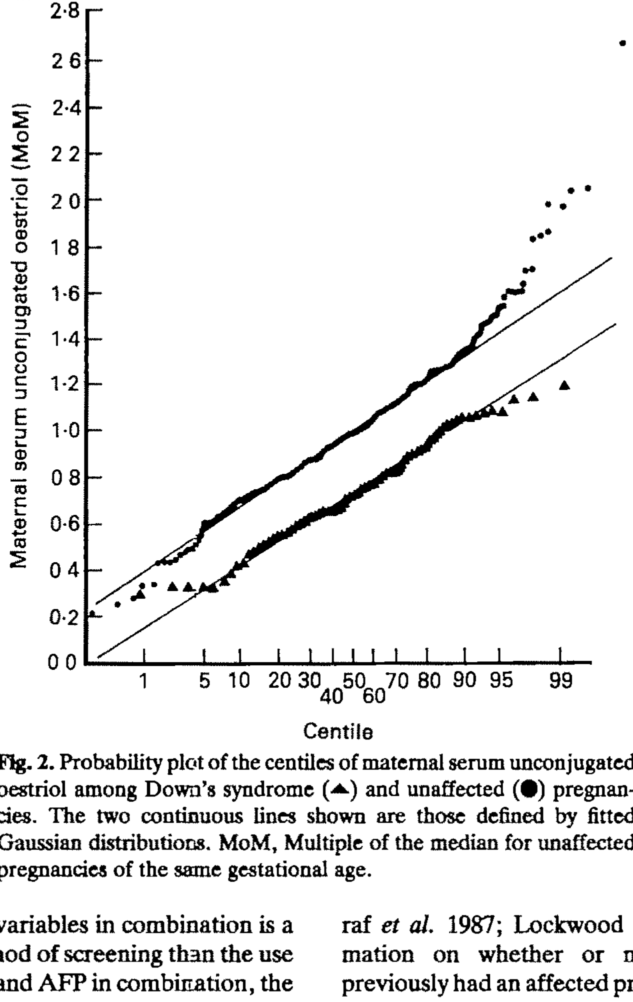

Fig. 2. Probability plot of the centiles of maternal serum unconjugated oestriol among Down's syndrome (▲) and unaffected (●) pregnancies. The two continuous lines shown are those defined by fitted Gaussian distributions. MoM, Multiple of the median for unaffected pregnancies of the same gestational age.

all three screening variables in combination is a more effective method of screening than the use of age alone or age and AFP in combination, the method currently employed. The measurement of fetal femur length has also been shown to discriminate between affected and unaffected pregnancies and this information may further increase the effectiveness of screening (Benacerraf *et al.* 1987; Lockwood *et al.* 1987). Information on whether or not a woman has previously had an affected pregnancy can also be incorporated into the screening procedure but this will lead to only a very small increase in the detection rate.

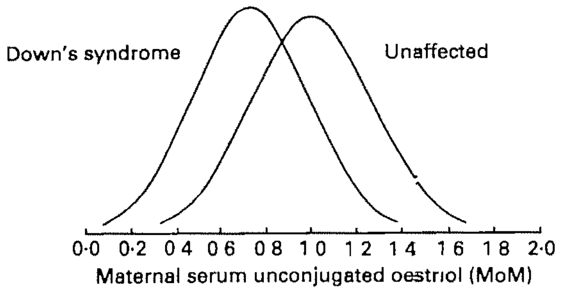

Fig. 3. Gaussian frequency distribution of maternal serum unconjugated oestriol levels in Down's syndrome and unaffected pregnancies. MoM, Multiple of the median for unaffected pregnancies of the same gestational age.

All three screening variables can be used in combination by extending the approach previously described for age and AFP (Palomaki & Haddow 1987; Cuckle *et al.* 1987) to include unconjugated oestriol. Using this approach each woman's risk of a Down's syndrome term pregnancy is estimated and if this is above a specified risk cut-off level her result is regarded as positive. Table 6 shows, for six specified risk cut-off levels from 1:100 to 1:350, the estimated detection rate, false-positive rate and average risk in women with positive screening results when maternal age and AFP are used in combination, age and unconjugated oestriol are used in combination and all three are used in combination. For example at a risk cut-off level of 1:250 the use of all three screening variables in combination would yield a detection rate of 45% with a

Table 3. Median maternal serum unconjugated oestriol level (MoM) in Down's syndrome and unaffected pregnancies according to maternal age

	Down's syndrome pregnancies		Unaffected pregnancies	
Maternal age at expected date of delivery (years)	Median unconjugated oestriol (MoM)	Number	Median unconjugated oestriol (MoM)	Number
<30	0·75	20	0·98	100
30–34	0·72	17	1·04	85
35–39	0·76	19	1·00	95
≥40	0·73	21	1·00	105
All	0·73	77	1·00	385

MoM, Multiple of the median for unaffected pregnancies of the same gestational age.

Table 4. Median maternal serum unconjugated oestriol level (MoM) in Down's syndrome and unaffected pregnancies according to maternal serum AFP level

	Down's syndrome pregnancies		Unaffected pregnancies	
AFP level (MoM)	Median unconjugated oestriol (MoM)	Number	Median unconjugated oestriol (MoM)	Number
≤0·60	0·66	17	0·74	22
0·61–0·80	0·72	24	0·95	76
0·81–1·00	0·82	23	0·96	94
>1·00	0·82	13	1·04	193
All	0·73	77	1·00	385

MoM, Multiple of the median for unaffected pregnancies of the same gestational age.

Table 5. False-positive rates (%), corresponding to specified Down's syndrome detection rates by screening using maternal age, serum AFP and serum unconjugated oestriol alone or in combination

	False-positive rate (%) using:					
Down's syndrome detection rate (%)	Age alone (a)	AFP alone (b)	Unconjugated oestriol alone (c)	Age and AFP (d)	Age and unconjugated oestriol (e)	Age, AFP and unconjugated oestriol (f)
60	31	33	28	20	14	12
55	25	28	19	16	11	9·1
50	19	24	16	12	8·8	7·0
45	15	20	13	9·8	6·7	5·3
40	11	17	11	7·3	5·0	3·9
35	7·5	14	8·5	5·3	3·7	2·8
30	5·1	11	6·6	3·6	2·5	1·9
25	3·3	8·2	5·0	2·2	1·6	1·2
20	1·9	6·0	3·5	1·3	0·9	0·7

A screening result is positive if (a) age is advanced, (b) AFP is low, (c) unconjugated oestriol is low, or for (d), (e) and (f) risk of Down's syndrome (at term) is high (see Appendix II for the formulae used in risk estimation).

Table 6. Down's syndrome detection rate, false-positive rate and average risk of Down's syndrome in positives by screening using maternal age, serum AFP and serum unconjugated oestriol in combination according to the risk cut-off level

	Age and AFP			Age and unconjugated oestriol			Age, AFP and unconjugated oestriol		
Risk cut-off level	Detection rate (%)	False-positive rate (%)	Average risk in positives	Detection rate (%)	False-positive rate (%)	Average risk in positives	Detection rate (%)	False-positive rate (%)	Average risk in positives
1:100	17	0·9	1.41	22	1·1	1 41	24	1 2	1:37
1·150	23	1·7	1·61	28	2 2	1 60	32	2·3	1.56
1 200	27	2·7	1.79	34	3 4	1·78	39	3·7	1.74
1:250	31	3·8	1:97	41	5 2*	1 101	45	5·2*	1.92
1 300	35	5 2	1.120	46	7·2	1 122	50	6·8*	1·109
1 350	39	6·7	1.140	51	9·1	1·141	54	8·5	1.125

A screening result is positive if the risk of Down's syndrome (at term) ⩾ the cut off

*Although these false-positive rates appear discrepant from those in Table 5 corresponding to detection rates of 45% and 50% they are in fact correct The differences are due to rounding in this table. The exact detection rates in this table are 44·7% and 49·5%, respectively

false-positive rate of 5·2%. To achieve the same detection rate using only maternal age and AFP in combination, a 1:430 risk cut-off level would be required and this would yield a false-positive rate of 9·8%; using only maternal age and unconjugated oestriol in combination, a 1:280 risk cut-off level would be required and this would yield a 6·7% false-positive rate.

The addition of serum unconjugated oestriol measurement to a Down's syndrome screening programme would be cost-effective; at any level of detection of Down's syndrome fewer women would need to have an amniocentesis. The savings would outweigh the extra cost of the oestriol estimations. For example, at a detection rate of 40% the addition of oestriol measurement to an AFP/age screening programme would mean that of every 1000 women screened 34 (3·4%, i.e. 7·3% less 3·9% from Table 5) would be saved an unnecessary amniocentesis, resulting in a financial saving that would be greater than the cost of the 1000 extra serum oestriol estimates. An assay that would measure maternal serum unconjugated oestriol and AFP simultaneously in the same specimen would further increase the cost-effectiveness of screening.

Acknowledgments

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References

Benacerraf, B R., Gelman, R & Frigoletto, F. D. (1987) Sonographic identification of second trimester fetuses with Down's syndrome *N Engl J Med* **317,** 1371-1376.

Canick, J. C., Knight, G J., Palomaki, G. E., Haddow, J E , Cuckle, H S & Wald, N. J (1988) Low second trimester maternal serum unconjugated oestriol in pregnancies with Down's syndrome. *Br J Obstet Gynaecol* **95,** 330-333

Cuckle, H. S , Wald, N J & Lindenbaum, R. H. (1984) Maternal serum alpha-fetoprotein measurement a screening test for Down syndrome. *Lancet* **i,** 926-929.

Cuckle, H S , Wald, N. J & Thompson, S G (1987) Estimating a woman's risk of having a pregnancy associated with Down's syndrome using her age and serum alpha-fetoprotein level. *Br J Obstet Gynaecol* **94,** 387-402.

Lockwood, C., Benacerraf, B R., Krinsky, A., Blakemore, K , Belanger, K., Mahoney, M & Hobbins, J (1987) A sonographic screening method for Down syndrome. *Am J Obstet Gynecol* **157,** 803-808

Palomaki, G E & Haddow, J. E (1987) Maternal serum alpha-fetoprotein, age, and Down syndrome risk. *Am J Obstet Gynecol* **156,** 460-463

Royston, J P. (1983) Some techniques for assessing multivariate normality based on the Shapiro-Wilk W *Appl Statist* **32,** 121-133.

Siiteri, P K. & MacDonald, P. C. (1966) Placental estrogen biosynthesis during human pregnancy. *J Clin Endocrinol Metab* **26,** 751-761

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Appendix

I *Bivariate Gaussian frequency distribution of serum unconjugated oestriol and log AFP*

The Shapiro–Wilk *W*-test was applied to squared radii as described by Royston (1983). This involves the calculation of omega, a variable which will be normally distributed with mean zero and standard deviation unity if the distribution of unconjugated oestriol and log AFP is bivariate Gaussian. For Down's syndrome pregnancies the value of omega was $-0{\cdot}72$ ($P=0{\cdot}76$) and for unaffected pregnancies omega was $1{\cdot}30$ ($P=0{\cdot}10$) after excluding 10 outlying values. The analysis showed that there was no statistically significant deviation from a bivariate Gaussian distribution.

II *Risk of Down's syndrome term pregnancy for a specific maternal age, serum unconjugated oestriol level (x) and serum AFP level (y)*

The risk of Down's syndrome was expressed as an odds ratio of $1{:}u$ where u is the number of unaffected births that occur for each Down's syndrome birth. The risk for a specific maternal age and (i) serum unconjugated oestriol, (ii) serum AFP or (iii) both was estimated from the age-specific risk in years (given in Table 1 of Cuckle *et al.* 1987), the left hand side being multiplied by either:

(i) $(S_U/S_D)\exp[(Z_U^2 - Z_D^2)/2]$;

(ii) $(S'_U/S'_D)\exp[((Z'_U)^2-(Z'_D)^2)/2]$; or

(iii) $(S_US'_U)/S_DS'_D)\quad\surd((1-R_U^2)/(1-R_D^2))\quad\exp[(V_U-V_D)/2]$

where: $V_D = (Z_D^2-2R_DZ_DZ'_D + (Z'_D)^2)/(1-R_D^2)$; $V_U = (Z_U^2-2R_UZ_UZ'_U + (Z'_U)^2)/(1-R_U^2)$; $Z_D = (x-M_D)/S_D$; $Z'_D = (\log_{10}(y)-M'_D)/S'_D$; $Z_U = (x-M_U)/S_U$; $Z'_U = (\log_{10}(y)-M'_U)/S'_U$; $\exp[a] = e^a$; M_D, S_D, M_U and S_U are the means and standard deviations of unconjugated oestriol in Down's syndrome and unaffected pregnancies respectively after allowing for long term assay imprecision (see Results); M'_D, S'_D, M'_U, S'_U are the corresponding values for $\log_{10}$ AFP ($-0{\cdot}1427$, $0{\cdot}2052$, $0{\cdot}0000$ and $0{\cdot}2024$ respectively, see footnote to Table 2 in Cuckle *et al.* 1987); R_D and R_U are the correlation coefficients of unconjugated oestriol and $\log_{10}$ AFP values in Down's syndrome and unaffected pregnancies respectively ($0{\cdot}14$ and $0{\cdot}13$ respectively estimated from $C_D/(S_DS'_D)$ and $C_U/(S_US'_U)$ where C_D and C_U are the observed covariances).

For unconjugated oestriol values outside the range 0·40–1·40 MoM and AFP values outside the range 0·40–2·50 MoM the risk was estimated at the lower endpoint and described as greater than this or at the upper endpoint and described as less than this as appropriate.

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Trophoblast membrane infusion for unexplained recurrent miscarriage

P. M. JOHNSON, K. V. CHIA, C. A. HART, H. B. GRIFFITH,
W. J. A. FRANCIS

Summary. A novel protocol is described which has been developed for immunotherapy in unexplained recurrent miscarriage. This is based on a single intravenous infusion with isolated placental trophoblast plasma membrane vesicle preparations. Clinical experience gained with this approach is described. A total of 16/21 (76%) patients who subsequently had pregnancies have now achieved a live birth or are currently pregnant at greater than 28 weeks gestation.

Recurrent miscarriage is a common problem thought to have many possible causes, although recent immunological and immunogenetic evidence has focused attention towards an immunological background for a significant proportion of patients with unexplained recurrent miscarriage (Beer *et al.* 1985; Johnson *et al.* 1985*a*; McIntyre *et al.* 1986). Various concepts have been proposed whereby, in normal pregnancy, fetal antigens expressed at materno-fetal interfaces may actively recruit or induce maternal cellular and humoral immunoregulatory mechanisms protecting the fetal graft *in utero* (Faulk & McIntyre 1981; Johnson & Stern 1986). This maternal immunological recognition may be impaired in occasional women who consequently suffer recurrent miscarriage because of restricted protection from transplantation rejection afforded to the early embryo (Johnson *et al.* 1986).

Recent studies have suggested that active allogeneic immunization with peripheral blood leucocytes may favour subsequent reproductive success for these patients (Beer *et al.* 1985; Taylor *et al.* 1985; Mowbray *et al.* 1985; Takakuwa *et al.* 1986). The source (paternal or third-party cells), route of administration and dose have varied between centres, as have selection criteria for patient inclusion. Although convenient, this approach has limitations because of risks of maternal sensitization to HLA, erythrocyte or platelet antigens, perinatal host-versus-graft disease (Editorial 1983), and transfusion-related risks including viral transmission by viable leucocytes (e.g. CMV; Radcliffe *et al.* 1986). Severe fetal growth retardation in pregnancy and fetal congenital abnormalities have been reported after leucocyte immunization (Beer *et al.* 1985; Cauchi *et al.* 1987). In addition, depending on the approach employed, Rhesus-negative patients may need to be protected with anti-D globulin or large numbers of donors may require screening to find donors with compatible blood group antigen phenotypes (Taylor *et al.* 1985).

An alternative approach to immunization with intact live HLA-positive leucocytes is to mimic fetal antigen presentation in normal pregnancy by the use of trophoblast surface antigens.

University of Liverpool, PO Box 147, Liverpool L69 3BX, UK
Department of Immunology
P. M. JOHNSON *Professor of Immunology*
K. V. CHIA *Clinical Research Fellow*

Department of Medical Microbiology
C. A. HART *Professor of Medical Microbiology*

Warrington General Hospital, Warrington WA5 1QG
H. B GRIFFITH *Consultant Obstetrician and Gynaecologist*

Liverpool Women's Hospital, Catherine Street, Liverpool L8 7NJ
W J. A FRANCIS *Consultant Obstetrician and Gynaecologist*

Correspondence· Professor P M Johnson

This is the basis of the present study which has established novel techniques for single intravenous infusion with isolated placental trophoblast plasma membrane vesicle preparations. We report results to date using this approach in women with unexplained recurrent miscarriage.

Patients and methods

Women were included in this study with three or more consecutive confirmed first-trimester miscarriages of unknown aetiology, each by a single partner, with either no live birth (group A) or a single live birth in the first pregnancy (group B). Chromosomal, anatomical, microbiological, hormonal and other medical reasons (e.g. diabetes) for recurrent miscarriage had been excluded as far as possible; investigations included a hysterosalpingogram, thyroid function tests, cervical cultures and karyotypic analyses. Patients were excluded if they had a blood relative known to have had two or more unexplained miscarriages or if they had serum lymphocytotoxic antibody (LCA), acquired anti-red cell antibody, anti-nuclear autoantibody (ANA) or lupus anticoagulant autoantibody activity (assessed by prolonged activated partial thromboplastin clotting time (APTT) and anti-cardiolipin antibody measured by ELISA). Patients with a total serum IgE level of >1000 i.u./ml were also excluded, whereas patients with a total serum IgE level of 100–1000 i.u./ml were skin prick-tested with a 1:10 dilution in pyrogen-free saline of the final trophoblast membrane preparation immediately before intravenous infusion. All women had a normal total and differential peripheral blood cell count. The HLA phenotypes of the couple were not taken into account, and women were not considered for infusion if known to be pregnant.

Isolated trophoblast membrane vesicle preparations

Term placentas were collected at delivery, where possible from caesarean sections, from healthy caucasian pregnancies with no known history of infection. Retroplacental blood was tested for HBsAg, antibodies to HIV and to *Treponema pallidum;* parental ABO and Rh blood groups were noted. All subsequent manoeuvres were performed in a laminar air-flow cabinet under strict aseptic conditions.

Placental syncytiotrophoblast microvillous plasma membrane (StMPM) vesicle preparations (Ogbimi *et al.* 1979; Webb *et al.* 1985) were isolated essentially as originally described by Smith *et al.* (1974). Each placenta was stripped of the cord, membranes and adherent decidual tissue. The remaining villous tissue was cut into small pieces and washed gently at 4°C with isotonic calcium chloride. All buffers were prepared with sterile pyrogen-free distilled water and contained antibiotics (penicillin, 100 000 U/l; streptomycin, 100 mg/l). After repeated washing and sieving, these tissues were finely cut and 500 ml sterile pyrogen-free saline was added. This was left to stir gently for 60 min at 4°C in a covered flask. The mixture was then sieved and the resultant solution centrifuged for 10 min at 15 000 ***g***. The supernatant was finally centrifuged for 1 h at 100 000 *g* to obtain the final StMPM vesicle pellets.

These membrane pellets were resuspended in sterile pyrogen-free saline and u.v.-irradiated as a thin film for 45 min using a 15 W germicidal u.v.-source at a distance of 10 cm. They were then washed by ultracentrifugation (1 h at 100 000 ***g***) to remove antibiotics, and re-homogenized in a mixture of sterile citrate-phosphate-dextrose (4 ml) and saline (16 ml) before being lyophilized for storage. For use, each sample was reconstituted with 20 ml sterile pyrogen-free distilled water, thoroughly homogenized and centrifuged at 3000 *g* for 10 min to remove any aggregated material.

Small StMPM aliquots taken before and after the u.v.-irradiation, as well as the reconstituted material, were assessed microbiologically by examination for cytopathic effect on Vero cell monolayers at 37°C for up to 72 h and by inoculation into Robertson's cooked meat broth and incubation at 37°C for 24 h. The broths were subcultured onto enriched solid media and incubated at 37°C anaerobically and in 7% CO_2 in air. Plates were examined at up to 48 h incubation. Of 125 preparations, 16 (13%) were unsuitable for use, mostly because of contamination by *Pseudomonas maltophilia.* Small aliquots of the final sample were also tested for thromboplastin activity by standard techniques and discarded if the activity was more than an equivalent volume of platelets from an infusion pack.

Intravenous injection of BALB/c mice with 2 mg wet weight (approx. 0·2 mg protein) sterile ^{125}I-radiolabelled trophoblast membrane

(StMPM) preparations in 0·2 ml saline resulted in >95% body clearance by 24 h and no atypical histopathology in animals killed at 24–72 h. Similar results were also obtained in nude mice and StMPM-presensitized BALB/c mice. Analysis of blood coagulation in the New Zealand rabbits injected intravenously with 500 mg (approx. 50 mg protein) sterile StMPM in 10 ml saline over 10 min showed no significant consumption of coagulation factors or change in platelet count for up to 24 h. There were no local reactions, and post-mortem histopathology showed no difference compared with age-matched unimmunized animals.

Trophoblast membrane infusion

Local ethics committee approval was obtained, as well as informed consent from all patients. Intravenous infusion with 1 g wet weight StMPM preparation (approx. 100 mg total protein), obtained from two separate preparations from donors who were blood-group matched with the recipient, was performed by slow infusion from a 250 ml saline drip-pack over a period of 1–2 h. All patients had a full blood count and coagulation times estimated before, during and after the infusion. Blood pressure, pulse and temperature were repeatedly monitored. All women were advised to wait 1–3 months after the infusion treatment before considering conception, depending on whether they had anti-cytomegalovirus (CMV) antibody (Radcliffe *et al.* 1986). They were not pressured to conceive as soon as possible.

Results

Trophoblast membrane infusion has been performed in 50 women with recurrent miscarriage (22 in group A and 28 in group B) in an initial study which started in December 1982. No adverse clinical or haematological reactions to the infusion have been noted. Twenty-four patients have not yet become pregnant, mostly since infusion was only conducted within the past year although three have adopted children and several continue to have secondary infertility known to be present before infusion. Five patients are currently in the first trimester of pregnancy. Twenty-one patients have had one or more pregnancies following trophoblast membrane infusion, and for whom pregnancy outcome is known or they are currently at greater than 28 weeks gestation. Their results are detailed in Table 1 (group A) and Table 2 (group B). Of these 21 women, 16 (76%) have now had a live birth or are at greater than 28 weeks gestation. No correlation was evident between pregnancy outcome and time interval from infusion to conception (Tables 1 & 2). The total male:female infant ratio was 10:6. There have been no cases of intrauterine growth retardation, nor any postnatal or developmental problems with any live-born child other than the premature first child of patient 6 in group A (Table 1).

All patients have been screened 4–6 weeks after infusion for serum ANA, for acquired red cell antibodies and for LCA against a panel of lymphocytes from 30 donors embracing the major HLA-A and B specificities; these were negative in all cases. Similarly, no patient developed unexpectedly elevated total serum IgE levels or showed seroconversion for either anti-CMV or anti-HSV antibodies. Serum antibodies reactive with detergent-solubilized StMPM protein could not be detected using a solid-phase enzyme-linked immunosorbent assay (ELISA) system in the women after trophoblast membrane infusion.

More unexpected complications occurred in group A (no live birth) than in group B (one live birth). Two patients (nos 7 and 8) suffered sudden 17-week miscarriages in their next pregnancies; these were ascribed to cervical incompetence (Table 1). Indeed, patient no. 7 had a further pregnancy during which a Shirodkar suture was inserted at 14 weeks, and the pregnancy went normally to term; she had not previously maintained a pregnancy beyond 11 weeks gestation. One patient (no. 9) suffered two further miscarriages after the infusion treatment (Table 1); although ANA-negative and anti-cardiolipin antibody-negative, with no evidence of SLE or a thrombotic history, she developed a prolonged activated partial thromboplastin clotting (APTT) in the first pregnancy suggestive of a lupus anticoagulant-type antibody activity (Lubbe & Liggins 1985). There was hypertension and proteinuria in the second pregnancy, which miscarried at 24 weeks despite prednisone and low-dose aspirin treatment. One other patient (no. 6) had a healthy normotensive pregnancy to 28 weeks when she presented complaining of reduced fetal movements. Cardiotocographs showed fetal compromise and a female infant was born by caesarean

Table 1. Summary of subsequent pregnancies in women with recurrent Miscarriage and no live births (group A) after trophoblast membrane infusion

Patient	Age (years)	Gravida	Para	Interval between infusion and conception (weeks)	Outcome of pregnancy
1	31	3	0	(i) 7	Normal term delivery; 4·18 kg female
				(ii) 78	Normal term delivery, 3·98 kg female
2	24	5	0	62	Normal term delivery, 3·90 kg male
3	26	3	0	1	Normal term delivery, 3·10 kg male
4	26	3	0	31	Spontaneous delivery (36 weeks), 2·14 kg male
5	33	3	0	46	Normal term delivery; 4·25 kg male
6	24	4	0	(i) 7	Caesarean section (28 weeks); 1·17 kg female, died at 3 weeks with neonatal complications
				(ii) 50	Spontaneous delivery (34 weeks), 2·05 kg female
7	32	5	0	(i) 24	17 week miscarriage; cervical incompetence
				(ii) 54	Normal term delivery; 3·41 kg male
8	32	5	0	27	17 week miscarriage; cervical incompetence
9	34	7	0	(i) 20	13 week miscarriage; raised APTT
				(ii) 86	24 week miscarriage; persistent proteinuria and hypertension
10	35	6	0	−1	10 week miscarriage
11	30	3	0	26	10 week miscarriage

section, the baby weighed 1·17 kg (appropriate for gestational age) (Table 1). The baby developed severe effects of prematurity and died with a Gram-negative septicaemia at 3 weeks. A subsequent pregnancy resulted in spontaneous delivery at 34 weeks of a live female baby. Three patients (nos 10, 11 and 21) had a repeat miscarriage after infusion treatment. All other patients had successful outcomes and patient no. 1 had two subsequent uncomplicated pregnancies.

Discussion

A novel programme for trophoblast membrane infusion has been successfully developed as an alternative to leucocyte immunization in women

Table 2. Summary of subsequent pregnancies in women with recurrent miscarriage after one live birth (group B) after trophoblast membrane infusion

Patient number	Age (years)	Gravida	Para	Interval between infusion and conception (weeks)	Outcome of pregnancy*
12	25	5	1	1	Normal term delivery, 3·68 kg male
13	28	5	1	15	Normal term delivery, 3·72 kg male
14	31	11	1	12	Normal term delivery, 3·81 kg male
15	39	6	1	15	Normal term delivery, 3·69 kg male
16	28	4	1	18	Normal term delivery; 3·58 kg female
17	25	4	1	10	Normal term delivery; 3 62 kg female
18	34	4	1	13	Chorioamnionitis (37 weeks), 2 80 kg male
19	35	4	1	7	Pregnant, 32 weeks
20	26	8	1	3	Pregnant, 28 weeks
21	33	11	1	4	9 week miscarriage

* September 1987

with unexplained recurrent miscarriage. Clinical experience with this approach has been described in this report and several points are worth highlighting. Great care was taken to ensure microbial sterility of isolated StMPM preparations. The possible effect of trophoblast membrane infusion on blood coagulation was assessed before, during and after slow infusion because of the thromboplastin activity of such material (Carson & Ramsey 1985). Cervical incompetence was subsequently identified in two patients, presumably as a result of previous multiple dilation and curettage procedures. The influence of such iatrogenic effects on viable pregnancies proceeding beyond the first trimester requires further clarification. No unexpected problems of induced subfertility have been encountered in this study.

Despite some complexity in data presentation, a total of 16 of 21 (76%) women with recurrent miscarriage who subsequently had pregnancies have now achieved a live birth or are currently pregnant at greater than 28 weeks gestation; this is comparable with leucocyte immunization (Mowbray *et al.* 1985; Taylor *et al.* 1985; Takakuwa *et al.* 1986) Interestingly, women with unexplained recurrent miscarriage who have had one live birth in their first pregnancy (Table 2) may fare better than those who have had no live births (Table 1). A placebo-controlled double-blind randomized study of trophoblast membrane infusion for unexplained recurrent miscarriage in women with no live birth was commenced in December 1985 and is in current progress.

Fetal syncytiotrophoblast microvillous plasma membranes (StMPM) have extensive contact with maternal blood in the human placenta, and syncytial elements continuously break away from the implantation site to enter the uterine vein without harmful effect in pregnancy (Attwood & Park 1961). Isolated StMPM vesicle preparations lack cell nuclear material and do not express HLA or blood group antigens (Johnson 1984). In addition, they can be stored as lyophilized material. Intravenous infusion with purified trophoblast membrane preparations mimics a situation in normal pregnancy proposed to result in immune recognition of fetal trophoblast antigens and development of protective immunoregulatory responses for the fetal allograft (Faulk & McIntyre 1981; Editorial 1983; Johnson & Stern 1986). However, the nature of the trophoblast antigens involved remains unclear although the trophoblast-leucocyte common (TLX) antigen is a candidate (Faulk & McIntyre 1981; Stern *et al.* 1986). The high frequency of spontaneous fetal resorption in a natural murine model of early pregnancy failure (CBA/J × DBA/2 mice) is known to be significantly reduced by maternal pre-immunization with leucocytes from some murine strains as well as with the C3H-B6 trophoblast cell line (Clark *et al.* 1986).

The approach of trophoblast membrane infusion or leucocyte immunization presupposes the subsequent development of a relevant immune response, which has been elusive to identify and monitor by laboratory assay. Indeed, serum anti-StMPM antibodies could not be detected by ELISA in our patients after trophoblast membrane infusion, although it should be stressed that such antibodies cannot usually be detected by this technique during normal pregnancy (Johnson *et al.* 1985*b*; Hole *et al.* 1987). Thus, the exact mechanism of action in unexplained recurrent miscarriage is unknown and could involve complex interactions between regulatory antibody, cellular or lymphokine responses to trophoblast and leucocyte surface components.

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References

Attwood, H. O. & Park, W.W (1961) Embolism to the lungs by trophoblast. *J Obstet Gynaecol Br Commonw* **68**, 611-617

Beer, A. E , Semprini, A E., Xiaoyn, Z & Quebbeman, J F. (1985) Pregnancy outcome in human couples with recurrent spontaneous abortion HLA antigen profiles, HLA antigen sharing, female serum MLR blocking factors and paternal leukocyte immunization. *Exp Clin Immunogenet* **2**, 137-153.

Carson, S D. & Ramsey, C A. (1985) Tissue factor (coagulation factor III) is present in placental microvilli and cofractionates with microvilli membrane proteins *Placenta* **6**, 5-12

Cauchi, M N., Koh, S. H., Tait, B., Mraz, G., Kloss, M & Pepperell, R J (1987) Immunogenetic studies in habitual abortion *Aust NZ J Obstet Gynaecol* **27**, 52-54

Clark, D. A , Chaput, A. & Tutton, D (1986) Active suppression of host-*vs*-graft reaction in pregnant mice VII Spontaneous abortion of allogeneic CBA/J × DBA/2 fetuses in the uterus of CBA/J mice correlates with deficient non-T suppressor cell activity. *J Immunol* **136,** 1668-1675

Editorial (1983) Maternal blocking antibodies, the fetal allograft, and recurrent abortion *Lancet* **ii.** 1175-1176.

Faulk, W. P & McIntyre, J. A. (1981) Trophoblast survival. *Transplantation* **32,** 1-5.

Hole, N., Cheng, H. M. & Johnson, P. M (1987) Antibody reactivity against human trophoblast antigens in the context of normal pregnancy and unexplained recurrent miscarriage? *Colloque INSERM* **154,** 213-224

Johnson, P. M (1984) Immunobiology of human trophoblast In *Immunological Aspects of Reproduction in Mammals* (Crighton, D B., ed), Butterworths, London, pp. 109-131

Johnson, P. M., Barnes, R M R., Risk, J. M , Molloy, C. M & Woodrow, J C (1985*a*) Immunogenetic studies of recurrent spontaneous abortion in humans. *Exp Clin Immunogenet* **21,** 77-83.

Johnson, P. M., Cheng, H M., Stevens, V. C. & Matangkasombut, P. (1985*b*) Antibody reactivity against trophoblast and trophoblast products *J Reprod Immunol* **8,** 347-352

Johnson, P. M , Chia, K V. & Risk, J. M. (1986) Immunological question marks in recurrent spontaneous abortion In *Reproductive Immunology 1986* (Clark, D A & Croy, B A., eds), Elsevier Biomedical Press, Amsterdam, pp. 239-245.

Johnson, P M & Stern, P. L (1986) Antigen expression at human materno-fetal interfaces. In *Progress in Immunology VI* (Cinader, B. & Miller, R. G., eds), Academic Press, Orlando, pp. 1056-1069.

Lubbe, W. F. & Liggins, G. C. (1985) Lupus anticoagulant and pregnancy. *Am J Obstet Gynecol* **153,** 322-327

McIntyre, J A., Faulk, W. P., Nichols-Johnson, V. R & Taylor, C. G (1986) Immunologic testing and immunotherapy in recurrent spontaneous abortion. *Obstet Gynecol* **67,** 169-175

Mowbray, J F., Gibbings, C , Liddell, H , Reginald, P W , Underwood, J L. & Beard, R. W (1985) Controlled trial of treatment of recurrent spontaneous abortion by immunisation with paternal cells. *Lancet* **i,** 941-943

Ogbimi, A. O , Johnson, P M , Brown, P J. & Fox, H. (1979) Characterization of the soluble fraction of human syncytiotrophoblast microvillous plasma membrane-associated proteins. *J Reprod Immunol* **1,** 127-140.

Radcliffe, J. J., Hart, C A , Francis, W J. A & Johnson, P. M (1986) Immunity to cytomegalovirus in women with unexplained recurrent spontaneous abortion *Am J Reprod Immunol Microbiol* **12,** 103-105

Smith, N. C., Brush, M. G. & Luckett, S (1974) Preparation of human placental surface membranes. *Nature* **252,** 302-303.

Stern, P L., Beresford, N., Thompson, S , Johnson, P M , Webb, P. D. & Hole, N (1986) Characterization of the human trophoblast-leukocyte antigenic molecules defined by a monoclonal antibody *J Immunol* **137,** 1604-1609

Takakuwa, K , Kanazawa, K & Takeuchi, S. (1986) Production of blocking antibodies by vaccination with husband's lymphocytes in unexplained recurrent aborters. the role in successful pregnancy *Am J Reprod Immunol Microbiol* **10,** 1-9

Taylor, C. G , Faulk, W P & McIntyre, J A. (1985) Prevention of recurrent spontaneous abortions by leukocyte transfusions *J R Soc Med* **78,** 623-637

Webb, P D., Evans, P W., Molloy, C M & Johnson, P. M (1985) Biochemical studies of human placental microvillous plasma membrane proteins *Am J Reprod Immunol Microbiol* **8,** 113-117

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Topographical distribution of prostaglandin E receptors in human myometrium

J. M. ADELANTADO, A. LÓPEZ BERNAL, A. C. TURNBULL

Summary. The binding of radiolabelled prostaglandin (PG) $F_{2\alpha}$ and PGE_2 by human myometrium was measured *in vitro* and the distribution and characteristics of the binding sites in non-pregnant and pregnant uteri were studied. $PGF_{2\alpha}$ binding sites were of low affinity (Kd 30 nM) and could be occupied by PG of the E series with higher affinity than $PGF_{2\alpha}$ itself. PGE binding sites were of high affinity (Kd 1·5 nM) and highly specific for PG of the E series, suggesting that they represent true PGE receptors. The concentration of PGE receptors was higher in non-pregnant than in pregnant uteri at term. In non-pregnant uteri the concentration of PGE receptors was highest in the fundus and decreased towards the cervix; in term pregnant uteri the concentration was constant in all areas. In both non-pregnant and pregnant uteri there was a significantly lower PGE binding affinity in cervix than in myometrium from the fundus-corpus area. The concentrations and affinity of PGE receptors were similar during the proliferative and secretory phases of the menstrual cycle and were not influenced by age of the patient. PGE receptors were not influenced by the presence or absence of primary dysmenorrhoea but appeared to be increased in unexplained menorrhagia.

There is evidence from both in-vitro and in-vivo studies that prostaglandins act on the human uterus. Prostaglandin (PG) E_2 and $PGF_{2\alpha}$ stimulate myometrial contractility directly, probably by increasing intracellular calcium concentrations (Carsten 1973; Villar *et al.* 1985). Prostaglandins can also potentiate the stimulatory effects of compounds such as oxytocin and catecholamines by modulating nucleotide levels in myometrial cells (Bhalla *et al.* 1972; Vesin & Harbon 1974). During pregnancy, PG administration can induce uterine contractions at any gestation and PG synthesis inhibitors can inhibit uterine contractions in preterm labour. Furthermore, PGE_2 has been used extensively to ripen the cervix before mid-trimester terminations and before induction of labour. While the action mechanism of prostaglandins on the human uterus has not been completely elucidated, it is believed that they interact with specific receptors on cell membranes (Wakeling & Wyngarden 1974; Carsten & Miller 1981). The purpose of this study was to measure the concentration and affinity of such receptors in uteri obtained during the follicular and luteal phases of the menstrual cycle and during pregnancy.

Nuffield Department of Obstetrics and Gynaecology, John Radcliffe Hospital, Headington, Oxford OX3 9DU
J. M ADELANTADO *Lalor Postdoctoral Fellow*
A. LÓPEZ BERNAL *Research Fellow*
A. C. TURNBULL *Professor*
Correspondence: A. López Bernal

Patients and methods

Uterine specimens from premenopausal women were obtained at hysterectomy performed for gynaecological indications such as menorrhagia, secondary dysmenorrhoea not associated with uterine fibroids, infarcts or endometriosis, and sometimes as a sterilizing procedure in multiparous women with functional menorrhagia or dysmenorrhoea. The phase of the menstrual cycle was ascertained from the clinical history and by histological dating of the endometrium. Pregnant uteri were obtained from three women undergoing hysterectomy at 12–16 weeks gestation and from four women having caesarean hysterectomies at term because of uterine rupture in two and postpartum haemorrhage in the other two. In all cases, histology was normal. The tissues were obtained in accordance with the requirements of the Central Oxfordshire Research Ethics Committee.

Binding assays

^{3}H-PGF$_{2\alpha}$ and ^{3}H-PGE$_2$ binding was measured by a modification of the method of Cuatrecasas & Hollenberg (1976). Tissue samples (0·5–3 g) were frozen in solid carbon dioxide and stored at −70°C for up to 2 weeks without appreciable loss of binding. The tissues were defrosted, freed from endometrium and peritoneal layer, washed, minced and suspended (1/5, weight/volume) in 50 mM tris-HCl buffer, pH 7·4, containing 0·25 M sucrose, 0·5 mM CaCl$_2$, 1 mM ditiothreitol, 1% gelatin and 10 μM indomethacin. The tissues were disrupted with a ground glass conical homogenizer and the resultant homogenates were filtered through four layers of surgical gauze. Homogenates were centrifuged at 1000 *g* for 15 min and the supernatants centrifuged at 50 000 *g* for 60 min. The resultant membrane pellets were washed twice in fresh buffer and resuspended to a protein concentration of about 0·5 mg/ml.

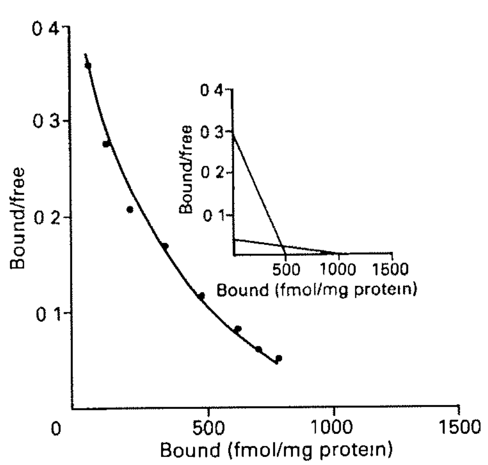

Fig. 1. Characteristics of ^{3}H-PGE$_2$ binding to human myometrium. The points represent specific binding as described in the text. The inset represents a transformation of the data by the method of Rosenthal (1967).

Incubations were carried out with varying concentrations (0·25–25 nM) of either [5, 6, 8, 9, 11, 12, 14, 15, (n)-^{3}H]-PGF$_{2\alpha}$, 6·7 TBq/mmol or [5, 6, 8, 11, 12, 14, 15, (n)-^{3}H]-PGE$_2$, 5·9 TBq/mmol (Amersham International), with and without a 1000-fold excess of the corresponding non-labelled PG (Upjohn Ltd, Kalamazoo) in a final volume of 0·15 ml. Optimal binding was achieved after 30 min at 37°C for ^{3}H-PGF$_{2\alpha}$ and after 45 min at 20°C for PGE$_2$ (Adelantado 1985). At the end of the incubation 0·1 ml samples were filtered through Whatman GF/B discs and the radioactivity measured. Specific binding was calculated as the difference between total binding and non-specific binding (binding in the presence of excess non-labelled PG). Non-specific binding averaged 10% of total binding The concentration of binding sites and their affinity (Kd) was calculated from Scatchard plots (Scatchard 1949). Most Scatchard plots were rectilinear, suggesting a single class of binding sites; however, in some cases (Fig. 1) a second component of lower affinity could be detected with ^{3}H-PGE$_2$ as ligand and it was substracted from the higher affinity component by the method of Rosenthal (1967). Binding affinities for several prostanoids were estimated in three different membrane preparations incubated with 7·5 nM of radiolabelled ligand and increasing concentrations (1 nM–100 μM) of unlabelled competitor. Relative binding affinities were calculated as the ratio of the mass of unlabelled ligand (PGE$_2$ or PGF$_{2\alpha}$) required to reduce total binding by 50% to the mass of competitor required to reduce total binding by 50%, multiplied by 100.

In three experiments, at the end of the incubation ^{3}H-PGF$_{2\alpha}$ or ^{3}H-PGE$_2$ were extracted and chromatographed by HPLC as described by Demers *et al.* (1984). No significant metabolism of either ligand was detected. Protein concentration was estimated by the method of Bradford (1976). Statistical differences were assessed by the Mann–Whitney, Kruskal–Wallis and Friedman tests

Results

^{3}H-PGF$_{2\alpha}$ binding

The mean apparent Kd estimated in samples from the corpus from five non-pregnant uteri was 27 (SD 8) nM and the concentration of binding sites was 688 (SD 340) fmol/mg protein. No specific binding was detected in samples of cervix. Apparent Kd and concentration values in samples from pregnant uteri at term were: corpus 24 (SD 9) nM, 369 (SD 168) fmol/mg protein (n =4); cervix 32 (SD 23) nM, 424 (SD 302) fmol/mg protein (n = 4). These values were not significantly different from those obtained in non-pregnant uteri, except that cervical binding was present only in samples from pregnant uteri.

The relative binding affinity of several prostanoids for ^{3}H-PGF$_{2\alpha}$ binding sites was: PGF$_{2\alpha}$ 100; PGE$_1$ 1250; PGE$_2$ 1070; PGA$_2$ 110; 13–14 dihydro PGF$_{2\alpha}$ 38; thromboxane B$_2$ and 15-oxo-PGF$_{2\alpha}$ <1.

^{3}H-PGE$_2$ binding

In non-pregnant uteri ^{3}H-PGE$_2$ binding was studied in relation to age, phase of the menstrual cycle and gynaecological disorder; all myometrial samples were taken from the corpus uteri. The results are presented in Table 1. There were no differences in the concentration or affinity of PGE receptors in relation to age or phase of the cycle. Women complaining of dysmenorrhoea had similar receptor levels to those found in women who underwent hysterectomy for other reasons. Menorrhagic women had higher receptor concentrations than women who underwent hysterectomy for reasons other than menorrhagia, although this difference was not statistically significant. The affinity of the receptors was similar in all groups.

PGE receptors in mid-trimester uteri were of high affinity in the corpus, Kd 2·6 (SD 0·8) nM, and of low affinity in the cervix, Kd 39·8 (29·1) nM. The concentration of receptors (fmol/mg protein) was 447 (SD 231) in the corpus and 420 (SD 249) in the cervix (n = 3 for all).

Topographical distribution of ^{3}H-PGE$_2$ binding sites

Uteri from eight non-pregnant women (four in the follicular and four in the luteal phase of the cycle) and from four pregnant women at term were sliced at five equidistant points from fundus to cervix and the concentration of PGE$_2$ receptors was measured. The data presented in Fig 2 show that in non-pregnant uteri the binding was greatest in the fundus and corpus uteri and decreased towards the cervix ($P<0{\cdot}05$). Cervical binding was detectable only in the follicular phase but the apparent affinity [Kd 11·4 (SD 0·2) nM] was significantly lower ($P<0{\cdot}02$) than in the rest of the uterus (Kd range 0·5–3 nM) In pregnant uteri, high affinity binding (Kd 1·5–2·6 nM) was present in all myometrial samples but not in the cervix [Kd 19·4 (SD 8·4) nM]; the concentration of binding sites in the fundus-corpus area (range 222–270 fmol/mg protein) was lower than in non-pregnant uteri ($P<0{\cdot}05$).

The relative binding affinity of several prostanoids for myometrial ^{3}H-PGE$_2$ binding sites was: PGE$_2$ 100, PGE$_1$ 100, PGA$_2$ 40, 13,14-dihydro-PGE$_1$ 20, 13,14-dihydro-PGE$_2$ 15, 13,14-dihydro-PGF$_{1\alpha}$ 7, PGB$_2$ 1, PGB$_1$ 0·5, PGF$_{2\alpha}$ 0·5, 13,14-dihydro-15-oxo-PGE 0·5, 15-oxo-PGE$_1$, 13,14-dihydro-15-oxo-PGA, 15-oxo-PGE$_2$, PGF$_{1\alpha}$, 13-14-dihydro-15-oxo-PGF and thromboxane B$_2$ <0·5.

Table 1. PGE receptors in myometrium from non-pregnant women

Age group	No of women	Concentration (fmol/mg protein)	Kd (nM)
35–39	10	756 (236)	1·7 (0·5)
40–44	6	978 (297)	2·0 (0·6)
45–50	4	723 (165)	1·6 (0·4)
Menstrual phase			
Follicular	8	725 (248)	1·5 (0·2)
Luteal	12	843 (218)	1·7 (0·6)
Gynaecological disorder			
Dysmenorrhoea	6	852 (283)	1·5 (0·5)
Controls*	14	802 (209)	1·8 (0·8)
Menorrhagia	7	985 (208)	1·5 (0·6)
Controls†	13	783 (198)	1·6 (0·8)

Results are means (SD). * Women without dysmenorrhoea. † Women without menorrhagia

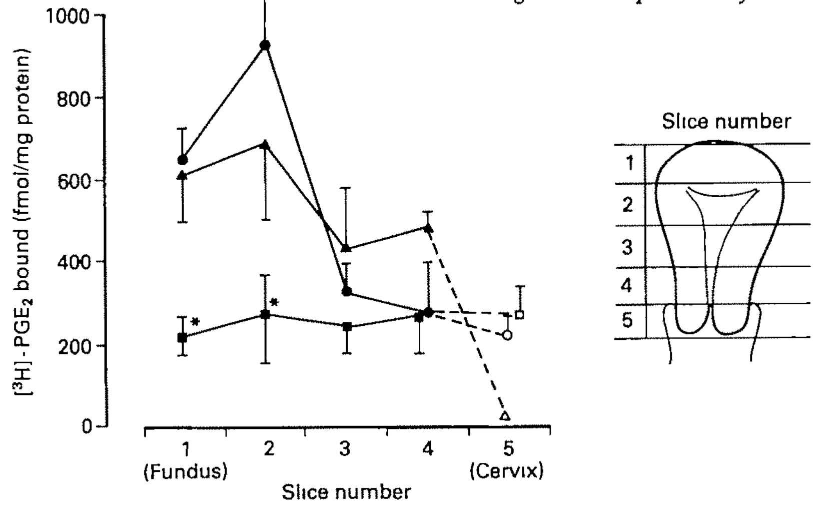

Fig. 2. Topographical distribution of PGE receptors in human non-pregnant and pregnant uterus. Each point represents the mean of four different patients and the bars represent SD. Binding in the cervix (open circles) was of significantly lower affinity than in the rest of the uterus. The asterisks indicate sections in pregnant uteri with significantly lower receptor concentrations than in non-pregnant uteri ●, Follicular phase, ▲, luteal phase; ■, pregnancy (term)

Discussion

This study confirms that the human uterus possesses PG receptors and that their affinity for PGE is about 10 times higher than for PGF$_{2\alpha}$ (Wakeling & Wyngarden 1974; Schillinger & Prior 1976). While the non-pregnant human myometrium responds consistently to PGF$_{2\alpha}$ by contracting, the effects on the cervix are more variable (Najak *et al.* 1970; Wiqvist *et al.* 1983). These responses are in accord with the distribution of ^{3}H-PGF$_{2\alpha}$ binding described in this paper: that receptors are present in the corpus but not in the cervix. Although pregnant uteri have PGF binding sites in both corpus and cervix, the concentration of these sites tends to be lower than in the non-pregnant uterus, possibly because there is a relatively greater increase in connective tissue in the uterus in pregnancy (Schwalm & Dubrauszky 1966; Hofmann *et al.* 1983); moreover the persistently high progesterone levels in pregnancy may lead to a decrease in binding sites. It is unlikely that these low affinity PGF binding sites are specific receptors, however, and it is possible that any action of PGF$_{2\alpha}$ in the human uterus is mediated through its interaction with PGE receptor sites (Schillinger & Prior 1976).

PGE binding sites were always demonstrable in human myometrium and their concentration was higher in non-pregnant samples than in samples from term pregnancy. Bauknecht *et al.* (1981) and Giannopoulos *et al.* (1985) have reported similar findings. In both pregnant and non-pregnant uteri we found high affinity sites in the fundus and corpus (areas of maximal smooth muscle cell concentration) and low affinity sites present mainly in the cervix. In non-pregnant uteri, the concentration of binding sites was highest in the fundus-corpus area, in agreement with the findings of Bauknecht *et al.* (1981), but this difference disappeared in pregnant uteri at term, as in the preliminary studies by Adelantado *et al.* (1985).

The high specificity of PGE binding sites, at least those in the myometrium, suggests they are true PG receptors. Accordingly, the high affinity binding sites could be responsible for the contracting effect of PGE while the low affinity sites in the cervix could mediate its remodelling, softening effect. The contractile effect on human pregnant and non-pregnant myometrium can be reproduced *in vitro* with PGE$_2$ doses of the same order as the Kd described here (Embrey & Morrison 1968; Wiqvist *et al.* 1983). Local, intravaginal administration of PGE$_2$ brings about cervical softening both in early and in term pregnancy. At term the effect of prostaglandin administration in the cervix can occur even during betamimetic induced tocolysis (Goeschen *et al.* 1985), suggesting that it is due to a direct effect of PGE$_2$ on the cervix and not secondary to uterine contractions. It therefore seems plausible to suggest that high affinity PGE receptors in human myometrium mediate the contractile effect of PG and that low affinity receptors in the cervix and in the connective tissue throughout the uterus are responsible for the development of cervical ripening and uterine compliance during pregnancy This simple two-receptor concept does not entirely explain the complex in-vitro pharmacological effects of PGE on the human uterus (Embrey & Morrison 1968; Wiqvist *et al.* 1983).

No differences have been found in the concentration or distribution of uterine PGE receptors during the follicular or luteal phase of the menstrual cycle. These findings are in accord with those of Hofmann *et al.* (1983) and of Giannopoulos *et al.* (1985) and suggest that PG receptors are not controlled by ovarian steroids. In contrast, Bauknecht *et al.* (1981) found that uterine PGE binding sites were increased in women taking oral oestrogens. In hamsters, uterine PGE receptors increase during oestrus (Wakeling *et al.* 1973).

No differences were found in uteri from women with severe dysmenorrhoea or from 'normal' women, in agreement with the findings of Hofmann *et al.* (1983). The physiopathology of dysmenorrhoea is obscure and it is possible that uterotocic agents other than PG are involved. It would be of interest to measure oxytocin and leukotriene receptors in this condition. Increased endometrial leukotriene release has been reported by Rees *et al.* (1987). Nevertheless, PG synthesis inhibitors are effective in the treatment of dysmenorrhoea (Anderson *et al.* 1976). The demonstration of increased myometrial PGE receptors in patients complaining of menorrhagia subjectively is in agreement with the study by Hofmann *et al.* (1983). However, the very poor correlation between subjective assessment of menstrual blood loss by the woman and objective measurement of menstrual loss (Chimbira *et al.* 1980) means that these data are of limited value. Nevertheless, we have recently demonstrated a significant correlation between measured menstrual blood loss and myometrial PGE receptor concentrations (Adelantado *et al.* 1988). Increased receptor levels and the reported shift from PGF to PGE production in the endometrium of menorrhagic women (Smith *et al.* 1981) suggests an altered response to PGE, a prostanoid also thought to have vasodilatory effects. Fenamates, a group of PG synthesis inhibitors which can effectively reduce menstrual blood loss, are thought to act at PG receptor level (Sanger & Bennett 1979), while pharmacological concentrations can displace PGE from human myometrial binding sites *in vitro* (R. Cañete Soler, unpublished observations).

Conclusion

This study confirms that human myometrium contains PG receptors which have 10 times greater affinity for PGE than PGF. The concentration of receptors is constant during the menstrual cycle and during reproductive age, although it is apparently reduced in pregnancy at term. The uterus is a target tissue for PGE but while our data show that PG receptors are not implicated in dysmenorrhoea, increased myometrial PGE receptors may play a part in the pathogenesis of unexplained menorrhagia. The pregnant uterus is very sensitive to PG. Increased PG production by intrauterine tissues is believed to initiate the spontaneous onset of labour (Casey & MacDonald 1986). It is therefore of interest that PGE is the principal prostanoid produced by the fetal membranes and binds with the highest affinity to myometrial receptors.

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References

Adelantado, J M. (1985) Hormonal studies in reproductive tissues. a receptor approach. MSc Thesis. University of Oxford

Adelantado, J. M., Humphries, J , López Bernal, A. & Turnbull, A. C. (1985) Is there a topographical distribution of prostaglandin E_2 receptors in the human pregnant uterus? In *The Physiological Development of the Fetus and Newborn* (Jones, C. T., Nathanielsz, P W , eds), Academic Press, London, pp 989-992.

Adelantado, J. M., Rees, C M P., López Bernal, A. & Turnbull, A. C (1988) Increased uterine prostaglandin E receptors in menorrhagic women. *Br J Obstet Gynaecol* **95**, 162-165.

Anderson, A B. M , Haynes, P J , Guilleband, J & Turnbull, A C (1976) Reduction of menstrual blood loss by prostaglandin synthetase inhibition. *Lancet* **i**, 774-776.

Bauknecht, T., Krahe, B , Rechenbach, U., Zahradnik, H. P. & Breckwoldt, M. (1981) Distribution of prostaglandin E_2 and prostaglandin $F_{2\alpha}$ receptors in human myometrium. *Acta Endocrinol* **98**, 446-450.

Bhalla, R L., Sanborn, B M. & Koreman, S. C. (1972) Hormonal interactions in the uterus: inhibition of isoproterenol-induced accumulation of adenosine 3', 5'-cycle monophosphate by oxytocin. *Proc Natl Acad Sci USA* **69**, 3761-3764.

Bradford, M. M. (1976) A rapid and sensitive method for the quantitation of nanogram quantities of protein utilising the principle of protein-dye binding. *Anal Biochem* **72**, 248-254.

Carsten, M. E (1973) Prostaglandins and cellular calcium transport in the pregnant human uterus. *Am J Obstet Gynecol* **117**, 824-832

Carsten, M. E & Miller, J D. (1981) Prostaglandin E_2 receptor in the myometrium: distribution in subcellular fractions. *Arch Biochem Biophys* **212**, 700-704

Casey, M L. & MacDonald, P. C. (1986) Initiation of labor in women. In *The Physiology and Biochemistry of the Uterus in Pregnancy and Labor* (Huszar, G. ed.), CRC Press, Inc , Boca Raton, Florida, pp. 155-161.

Chimbira, T. H , Anderson, A. B. M. & Turnbull, A C. (1980) Relation between measured menstrual loss and the patient's subjective assessment of loss, duration of bleeding, number of sanitary towels used, uterine weight and endometrial surface area. *Br J Obstet Gynaecol* **87**, 603-608.

Cuatrecasas, P. & Hollenberg, M. G (1976) Membrane receptors and hormone action. *Adv Protein Chem* **30**, 251-451.

Demers, L. M , Rees, M C. P & Turnbull, A. C (1984) Arachidonic acid metabolism by the nonpregnant uterus *Prostaglandins Leukotrienes Med* **14**, 175-180

Embrey, M P. & Morrison, M L. (1968) The effect of prostaglandins on human pregnant myometrium *in vitro*. *J Obstet Gynaecol Br Commonw* **75**, 829-832.

Giannopoulos, G., Jackson, K., Kredentser, J. & Tulchinsky, D. (1985) Prostaglandin E and $F_{2\alpha}$ receptors in human myometrium during the menstrual cycle and in pregnancy and labor. *Am J Obstet Gynecol* **153**, 904-910

Goeschen, K., Fuchs, A.-R., Fuchs, F., Rasmussen, A. B., Rehnstrom, J. V. & Saling, E. (1985) Effect of β-mimetic tocolysis on cervical ripening and plasma prostaglandin $F_{2\alpha}$ metabolite after endocervical application of prostaglandin E_2. *Obstet Gynecol* **65**, 166-171.

Hofmann, G. E., Rao, C. V , Barrow, G. H. & Sanfilippo, J. S. (1983) Topography of human uterine prostaglandin E and $F_{2\alpha}$ receptors and their profiles during pathological states. *J Clin Endocrinol Metab* **57**, 360-366.

Najak, Z., Hillier, R. & Karim, S S. M. (1970) The action of prostaglandins on the human isolated nonpregnant cervix. *J Obstet Gynaecol Br Commonw* **77**, 701-709.

Rees, M C. P., Di Marzo, V., Tippins, J. R., Morris, H. R. & Turnbull, A.C. (1987) Leukotriene release by endometrium and myometrium throughout the menstrual cycle in dysmenorrhoea and menorrhagia. *J Endocrinol* **113**, 291-295.

Rosenthal, H E (1967) A graphic method for the determination and presentation of binding parameters in a complex system *Anal Biochem* **20**, 525-532.

Sanger, G. J & Bennett, A (1979) Fenamates may antagonise the actions of prostaglandin endoperoxides in human myometrium. *Br J Clin Pharmacol* **8**, 479-484

Scatchard, G. (1949) The attractions of proteins for small molecules and ions. *Ann NY Acad Sci* **51**, 660-672.

Schillinger, E & Prior, G (1976) Characteristics of prostaglandin receptor sites in human uterine tissue. *Adv Prostaglandin Thromboxane Res* **1**, 259-263.

Schwalm, H & Dubrauszky, V (1966) The structure of the musculature of the human uterus—muscles and connective tissue. *Am J Obstet Gynecol* **94**, 391-404.

Smith, S. K , Abel, M. H., Kelly, R W. & Baird, D T. (1981) Prostaglandin synthesis in the endometrium of women with ovular dysfunctional uterine bleeding *Br J Obstet Gynaecol* **88**, 434-442

Vesin, M. F. & Harbon, S. (1974) The effects of epinephrine, prostaglandins and their antagonists on adenosine cyclic 3″, 5″-monophosphate concentrations and mobility of the rat uterus *Mol Pharmacol* **10**, 457-473

Villar, A., D'Ocon M. P & Anselmi, E. (1985) Calcium requirement of uterine contraction induced by PGE, importance of intra-cellular calcium stores. *Prostaglandins* **80**, 491-496.

Wakeling, A. E., Kirton, K. T. & Wyngarden, L. J. (1973) Prostaglandin receptors in the hamster uterus during the estrous cycle *Prostaglandins* **4**, 1-9.

Wakeling, A. E. & Wyngarden, L J. (1974) Prostaglandin receptors in the human, monkey and hamster uterus. *Endocrinology* **95**, 55-64.

Wiqvist, N., Lindblom, B., Wikland, M. & Wilhelmsson, L (1983) Prostaglandins and uterine contractility. *Acta Obstet Gynecol Scand* **113 (Suppl.)**, 23-29

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Artificial insemination with cryopreserved donor semen: a decade of experience

GABOR KOVACS, GORDON BAKER, HENRY BURGER,
DAVID DE KRETSER, DOUGLAS LORDING, JUNE LEE

Summary. Ten years' experience of artificial insemination with cryopreserved donor semen for 1023 courses in 783 women resulting in 572 pregnancies is reported. A simple approach with multiple inseminations timed on the basis of cycle length, temperature charts, mucus symptoms and signs was used. The life table pregnancy rate was 61% after 12 cycles of treatment and 75% after 24 cycles. Women had a significantly higher rate of pregnancy in second and subsequent courses of treatment, and the pregnancy rate for treatment beyond 12 cycles was significantly less successful. Women over 35 years of age were significantly less successful.

In Western countries sterility is considered to affect 5% of couples and in perhaps half of these, a male factor is responsible (Mosher & Pratt 1985; Borrie 1987). The options for these couples are adoption, child-free existence or artificial insemination with donor semen (AID). AID using fresh semen has been performed for many years with variable results (Kleegman 1953; Hill 1970; Robertson 1973; Glezerman 1981) The development of cryopreservation for human sperm in the 1960s facilitated marked expansion of AID services and large sperm banks have been established in many countries (Sherman 1985). The Reproductive Medicine Clinic at Prince Henry's Hospital commenced AID in 1975. By 1979, we had treated over 250 patients (Kovacs & Lording 1980). Our experience now involves over 1000 courses of insemination.

In November 1984, acquired immune deficiency syndrome (AIDS) became relevant to AID, and has necessitated quarantine of semen. Because of the resultant relative shortage of screened semen, the simple approach to timing inseminations by temperature charts and mucus symptoms has had to be abandoned, and this report was compiled at the end of an era.

Patients and methods

Over the 10 years to December 1984, 783 couples entered the programme. Of the 402 who achieved a pregnancy, 202 had a second course, 34 a third and four a fourth course of insemination. The majority had AID because of male infertility including azoospermia in 397, oligospermia in 284, other seminal abnormality (low motility and/or abnormal morphology) in 37 and unspecified causes in 54. For 11 couples AID was performed because of the risk of transmission of genetic diseases such as Huntington's chorea, and tuberous sclerosis Other reasons for insemination were sexual dysfunction such as impotence.

Before entering treatment, physical charac-

Reproductive Medicine Clinic, Medical Research Centre, Prince Henry's Hospital, St Kilda Road, Melbourne, Australia 3004
GABOR KOVACS
GORDON BAKER
HENRY BURGER
DAVID DE KRETSER
DOUGLAS LORDING
JUNE LEE

Correspondence: Gabor Kovacs

teristics of both partners were recorded and blood groups determined for donor matching. The female partner was assessed to determine the time of ovulation using cycle lengths, basal temperature charts, mucus symptoms and cervical score (Kovacs & Lording 1980). If there was any doubt about ovulation, progesterone was measured in the luteal phase and, where necessary, ovulation was induced with clomiphene, bromocriptine or human pituitary gonadotrophins (Kovacs *et al.* 1984). Immunity to rubella was checked. In the absence of a history suggestive of pelvic disease, the investigation of tubal patency was deferred until after three failed cycles of insemination.

The involvement of a medical social worker or counsellor has been an integral part of the programme. During the pretreatment assessment the couple are advised by the doctors about the nature of AID, given printed material explaining the procedure, and also consult the social worker for detailed discussions of the social, ethical and legal implications of AID (Clayton & Kovacs 1980).

Donors initially recruited were mainly medical students, but as the programme received more publicity, members of the general community volunteered to be donors. Prospective donors had a semen analysis performed using standard methods after 2 days of abstinence from ejaculation (Belsey *et al.* 1980). If the sperm concentration was >40 million/ml and sperm motility >50%, the man was invited to be a donor provided further screening tests were normal. Screening included bacteriological culture of semen for *Neisseria gonorrhoeae* and serological testing for syphilis, hepatitis B and sperm antibodies. Blood groups were also investigated for matching purposes. Physical characteristics—race, height, build, complexion and hair and eye colour were recorded with the donor code for subsequent use in matching with the recipient's husband.

Table 1. Inheritable diseases/traits

Thalassaemia
Colour blindness
Tay–Sachs disease
Haemophilia
Mental retardation
Huntingtons' chorea
Diabetes
Sickle cell trait
Phenylketonuria
Alkaptonuria
Eczema
Cystic fibrosis
Asthma
Epilepsy
Glaucoma
Parkinson's disease
Spina bifida
Any allergies, e.g. hayfever, or from eating certain foods, taking certain medication, or after contact with certain materials, etc.

Personal and family histories were obtained to exclude subjects with possible genetic disorders. A list of hereditary conditions was used for specific questioning (Table 1). The donors were counselled about the risks of transmitting venereal disease.

Our approach to confidentiality and secrecy of information about AID donors has changed with time. Initially it was decided that no information about the donor would be divulged to the recipient or child and thus little information on the donors was obtained. With changes in the general community attitudes to artificial conception (Kovacs *et al.* 1986) and freeing of information available to adoptees about their natural parents, we felt it desirable to obtain more information on the donors. This was supported by a survey of a group of donors who were in favour of non-identifying information being available to the AID parents if requested (Kovacs *et al* 1983). Consequently, a donor profile questionnaire was designed (Appendix).

Matching of the donor and recipient was undertaken on the basis of race, physical characteristics and blood group.

Donors produced semen specimens by masturbation in a special room adjacent to the laboratory. The specimens were allowed to undergo liquefaction, and an aliquot was taken for analysis. The remaining sample was mixed with an equal volume of egg yolk/glycerol cryoprotectant medium. The semen was then stored in straws, each containing 0·5 ml. The straws were cooled by two-stage freezing, either over nitrogen vapour followed by immersion into liquid nitrogen, or by automated programmable freezing machine (Pye-Daton Programmed Freezer). The frozen semen was then stored in liquid nitrogen in storage tanks (Mahadevan & Trounson 1980).

Each batch of stored semen was tested by determining post-thaw motility, and unsatisfactory specimens (post-thaw motility <40%) were discarded. Before insemination the 0·5 ml straw was left at room temperature for 10 min to allow the semen to thaw. One 0.5-ml specimen was used for each insemination. Inseminations were timed using the clinical factors of cycle length, temperature and mucus signs and symptoms. Usually, two to three daily inseminations were undertaken around the estimated time of ovulation.

Inseminations were either performed using a modified (shortened) bovine insemination gun, or by aspirating the thawed semen from a sterile container into a tuberculin syringe. Inseminations were pericervical, and the patients were asked to rest for 20 min after the procedure.

Analysis of outcome was by life-table methods (O'Connor & Trounson 1980).

Results

The outcome of 1023 courses of AID for up to 24 cycles of treatment resulting in 572 pregnancies is shown in Fig. 1. Approximately 50% of women were pregnant by 7 months, 61% by 12 months, 71% by 18 months and 76% by 24 months. The pregnancy rates for cycles 13–24 were much lower; to emphasize this, the life-table graph for the 13th–24th cycles is compared with the 1st–12th cycle curve in Fig. 2. Although the rate was lower, pregnancies still occurred in the second 12 months and others even occurred after 25 and 28 cycles (not shown). Overall, there is a progressive decline in pregnancy rates with time from 12% pregnant in the first cycle, 10% in the third, 8·3% in the 6th, 4.5% in the 9th, 4.5% in the 12th, and less than 3% after the 18th.

Pregnancy rates were significantly higher when women who previously conceived by AID returned for further treatment (Fig. 3). Of this group of women, 50% achieved pregnancy within four cycles, whereas in the first course of insemination, nine cycles were required for 50% to become pregnant.

The pregnancy rates were further analysed to determine the effect of the women's ages. Results of treatment for the 783 women were analysed, dividing the women into 5-year subgroups, at the time of commencing treatment. The distribution of women is shown in Table 2.

The four groups were compared to the overall results by log rank test. Both groups of over 30 years of age were significantly less successful than the total group, with the 31 to 35 year group ($\chi^2 = 4{\cdot}86$, $P<0{\cdot}05$) and the over 35 group ($\chi^2 = 6{\cdot}9$, $P<0{\cdot}01$).

Discussion

As AID is the only possible option for achieving pregnancy in many couples, its use has become widespread (Sherman 1985). This has been facilitated by the development of cryostorage, enabling screening and matching of donors.

As experience with AID increased, attempts have been made to simplify the treatment regimen. Initially, all women were screened for tubal patency before treatment, but on reviewing our first 252 treatments, we realized that half the pregnancies occurred in the first three cycles of inseminations, and subsequently have recom-

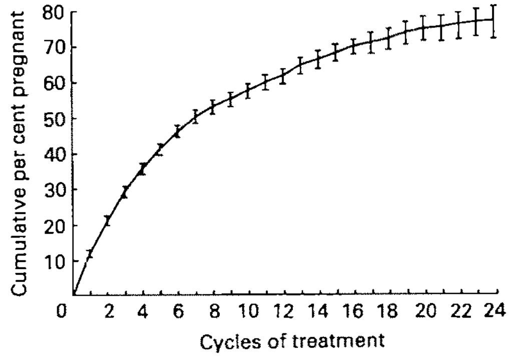

Fig. 1. Outcome of AID up to December 1984, life-table pregnancy rate curve of 1023 courses of AID.

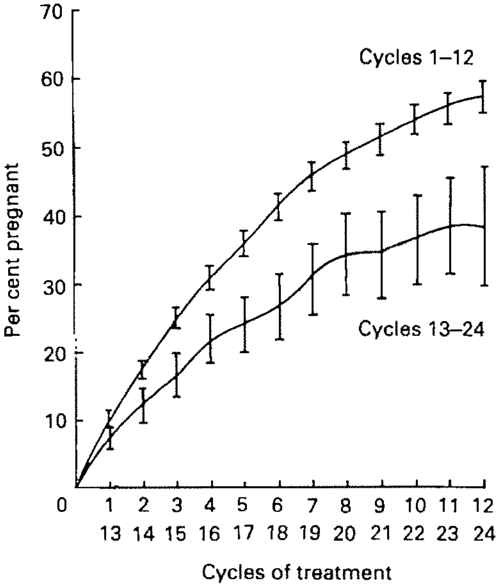

Fig. 2. Outcome of treatment by AID up to December 1984, comparison of life-table curves for cycles 13 to 24 and 1 to 12. $\chi^2 = 15{\cdot}1$, $P<0{\cdot}001$

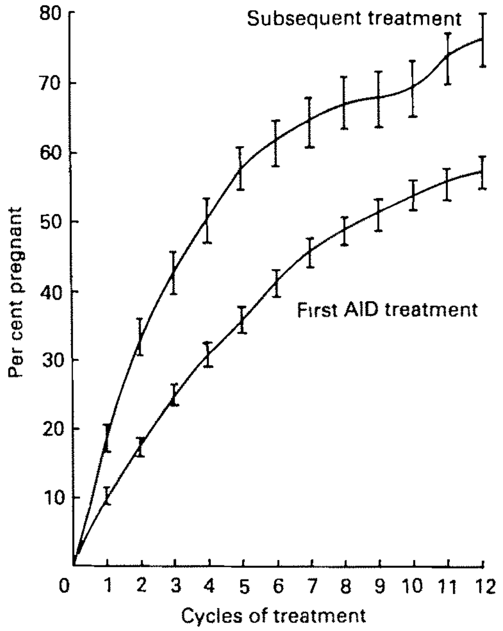

Fig. 3. Comparison of life-table curves for first course and subsequent courses after a pregnancy by AID up to December 1984. $\chi^2 = 31{\cdot}9$, $P<0{\cdot}001$.

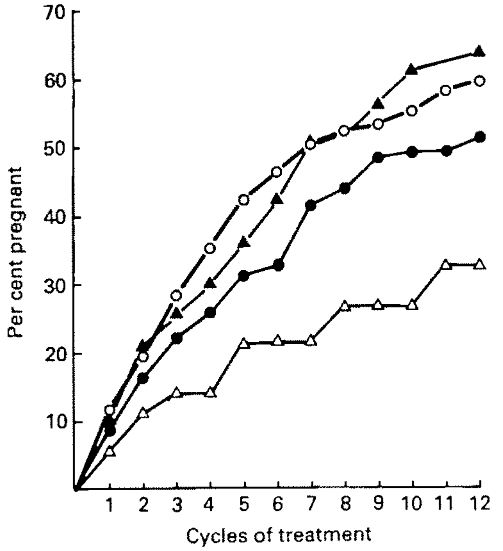

Fig. 4. Outcome of treatment by AID analysed with respect to age of recipient. ▲, <25 years; ○, 26–30 years; ●, 31–35 years; △, >35 years.

mended that tubal patency test be deferred until after three failed cycles, in women where there was no suspicion of pelvic pathology. However, as 80% of pregnancies are achieved within six cycles of treatment, we strongly recommend that laparoscopy be undertaken to exclude pelvic pathology after six failed cycles.

A social worker or counsellor has been part of our programme since its beginning. We have found that this is necessary because of the long-term social implications of the resultant conception. The counsellor also takes some of the workload from the clinicians as she discusses the social aspects with the patient. Our social worker has also been involved with the study of couples before treatment (Clayton & Kovacs 1980), the follow-up of offspring (Clayton & Kovacs 1982) and surveying of donors (Kovacs *et al.* 1983).

The ability to predict likely success is of benefit when counselling patients, and the use of life-table analysis allows this in a way that is easily understood. These life-tables enable us to advise patients that following a first pregnancy there is a significantly higher chance of conception occurring again. Similarly, we can also show that the chance of conception after 12 failed cycles is significantly decreased. Subsequently, we now advise patients to attempt in-vitro fertilization using donor sperm after 12 failed cycles of AID (Kovacs & Rogers 1984)

The appearance of the acquired immune deficiency syndrome (AIDS) has had a dramatic effect on AID programmes (Stewart *et al.* 1985). As the disease is transmitted by semen, there is a risk that if a donor who is a carrier of the AIDS virus is used, the infection may be spread to the recipients. With the inability to screen semen directly for the presence of the virus, indirect testing, for the presence of antibodies to human immune deficiency virus (HIV) in the blood has been introduced. The disadvantage of this is that antibodies do not appear until sometime after the incubation period, and during that period a donor could be HIV antibody negative, yet still carry the virus. To overcome this risk, a quarantine period for semen has been introduced. As the duration of the incubation period is yet unknown, quarantine periods of between 3 and 12 months have been recommended in different Australian states. We are quarantining semen for 6 months and this has resulted in a shortage

Table 2. Distribution by age of 783 women in the study

Age (years)	No. of women
<25	133
25–30	432
31–35	181
>35	37

of available semen, and all programmes have introduced waiting lists.

This paper summarizes our experience up to December 1984, when a simple approach to the timing and multiple inseminations has been used. With the necessity of quarantine, and subsequent shortage, we now confine ourselves to single inseminations after the luteinizing hormone (LH) peak.

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We would like to thank all the nursing, laboratory and administrative staff who have made this programme run so smoothly. We also thank our colleagues in the Reproductive Medicine Clinic for referring their patients, Ms Chris Clayton for her skills at counselling and Mrs J. Volfsbergs and Mrs J. Williams for typing this manuscript.

References

Belsey, M. A., Eliasson, R., Gallegos, A. J., Moghissi, K S., Paulsen, C A. & Prasad, M. R. N. (1980) *Laboratory Manual for the Examination of Human Semen Cervical Mucus Interaction.* Press Concern, Singapore.

Borrie, W. D. (1987) Fertility, mortality, infertility and generation replacement *Clin Reprod Fertil* (in press).

Clayton, C. E & Kovacs, G. T. (1980) AID—a pre-treatment social assessment. *Aust NZ J Obstet Gynaecol* **20**, 208-210.

Clayton, C. E & Kovacs, G T. (1982) AID offspring: initial follow-up study of 50 couples. *Med J Aust* **1**, 338-339

Glezerman, M. (1981) Two hundred and seventy cases of artificial donor insemination. management and results. *Fertil Steril* **35**, 180-187.

Hill, A S. (1970) Experiences with artifical insemination. *Aust NZ J Obstet Gynaecol* **10**, 112-114.

Kleegman, S. J. (1953) Therapeutic donor insemination. *Fertil Steril* **5**, 7-31.

Kovacs, G. T. & Lording, D. W. (1980) Artificial insemination with donor semen, review of 252 patients. *Med J Aust* **2**, 609-611.

Kovacs, G. T., Clayton, C. E & McGowan, M. P. (1983) The attitudes of semen donors. *Clin Reprod Fertil* **2**, 73-75.

Kovacs, G. T., Dennis, P. M., Shelton, R. J , Outch, K. D , McLean, R. A., Healy, D. L. & Burger, H. G. (1984) Induction of ovulation with human pituitary gonadotrophins: 12 years experience. *Med J Aust* **140**, 575-579.

Kovacs, G. T. & Rogers, P. (1984) IVF—a practical option when AID fails Proceedings of The Fertility Society of Australia, 3rd Annual Meeting, 1984, p. 2.

Kovacs, G T., Wood, C., Morgan, G C & Rawson, G. (1986) Community attitudes to artifical insemination by donor. *Aust Fam Physician* **15**, 50-51.

Mahadevan, M. & Trounson, A. O. (1980) Cryopreservation of human semen. In *Artificial Insemination by Donor* (Wood, C., Leeton, J & Kovacs, G , eds), Monash University Press, Melbourne, pp. 19-32

Mosher, W. D. & Pratt, W F. (1985) *Fecundity and Infertility in the United States, 1965–1982.* National Centre for Health Statistics Advance Data, No. 104 DHHS Public Health Service, Washington, US Government Printing Office

O'Connor, A. & Trounson, A. O. (1980) Assessment of artificial insemination success using life tables. In *Artificial Insemination by Donor* (Wood, C., Leeton, J & Kovacs, G., eds), Monash University Press, Melbourne, pp 33-37.

Robertson, S. (1973) Donor insemination—a substitute for the infertile male *Aust NZ J Obstet Gynaecol* **13**, 224-227

Sherman, J K (1985) Current status of clinical cryobanking In *Andrology, Infertility and Sterility* (Paulsen, C. A. *et al.*, eds), Academic Press, New York.

Stewart, G. J., Tyler, J. P. P., Cunningham, A L., Barr, J L , Driscoll, G L , Gold, J. & Lamont, B. J. (1985) Transmission of human T-cell lymphotrophic virus type III by artificial insemination by donor *Lancet* **ii**, 581-585

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Appendix

Donor Non-Identifying Information

A growing number of AID parents are planning to inform their children of the method of conception. The filling in of this background sheet will provide these children with adequate *non-identifying* information about their paternal background.

Date ___/___/___

Age 18–24 years ☐
25–29 years ☐
30–34 years ☐
35–40 years ☐

Married YES/NO

Number of existing children __________

Number of boys __________
Number of girls __________

Eye Colour ______	Weight ______
Hair Colour ______	Type of hair ______
Complexion ______	Do you tan easily? ______
Height ______	Country of birth ______
Build ______	

How would you describe yourself? (outgoing, placid, moody, sensitive, jolly, quiet, extroverted, introverted, etc.)

______

______

How do you get on with people? (parents, friends, boss, etc.)

______

______

How do you solve your personal problems and make decisions (quickly, after carefully exploring all points of view, with deliberation, etc.)

______

______

Level of schooling
Primary ☐
Secondary ☐
Tertiary ☐

List subjects most enjoyed ______

______

Did you like school? ______

What is your occupation? ______

What other types of jobs have you had? ______

______

What would you like to do in the future? ______

______

What do you like doing in your spare time? ______

______

Do you have any special talents? (eg, musical, artistic, sporting ability, creative skills)

______

______

Do you have good health? ______

If no, please give details ______

______

Have you had any operations? YES/NO

If so, what were they? ______

Are you allergic to anything? (eg, Penicillin, bee stings, pollen, dust, etc.)

____

____

Do you smoke? NO/YES How many? ________

Do you drink alcohol? NO/YES/A social drinker

Family History

Mother	*Father*
Eye Colour __________	Eye Colour __________
Height __________	Height __________
Age __________	Age __________
Hair Colour __________	Hair Colour __________
Build __________	Build __________
Complexion __________	Complexion __________
Nationality __________	Nationality __________

What level of schooling did she reach? ____________________

What is her occupation? ____________________

What level of schooling did he reach? ____________________

What is his occupation ____________________

Grandparents	Nationality
Mother's mother	__________
Mother's father	__________
Father's mother	__________
Father's father	__________

Brothers and Sisters

Sex	Age	Height (eg, short, medium, tall)	Comments

Would you like to meet any children which may result from AID once they reach 18 years of age?

Would like to meet ☐
Would definitely not like to meet ☐
Would not object if child wished to meet
but would not solicit a meeting ☐

In England where information is available to adoptive children on their biological parents only 10% of the children seek this information and only 1% actually wish to and do meet parents. Approximately 1% of adoptive children in Australia actually meet their biological parents through Jigsaw. It is anticipated that the percentages will be even less in the case of AID children.

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The treatment of normospermic infertility by gamete intrafallopian transfer (GIFT)

JOHN L. YOVICH, PHILLIP L. MATSON, DAVID G. BLACKLEDGE, SIMON R. TURNER, PETER A. RICHARDSON, JEANNE M. YOVICH, W. ROHINI EDIRISINGHE

Summary. Gamete intrafallopian transfer (GIFT) was applied in 207 treatment cycles in 73 couples. The pregnancy rate in cycles with only one (2/21, 9·5%) or two (2/29, 6·9%) oocytes transferred was significantly less than that in which four oocytes (36/116, 31·0%) were replaced. The collection of more than four oocytes did not influence the pregnancy rate in that treatment cycle. The overall pregnancy rate was 24·2% (50 of 207) and was similar in the four infertility groups studied (non-occlusive tubal disorders, endometriosis, cervical factor and unexplained infertility) with 28 (56%) of the pregnancies delivered at ≥20 weeks. The pregnancy wastage included 4 (8%) ectopic pregnancies and 3 (6%) late pregnancy losses. The 12 multiple pregnancies occurred following the transfer of three and four oocytes.

Many therapeutic techniques are now available for the treatment of infertile couples in which the female partner has patent fallopian tubes. Those procedures involving the manipulation of gametes include artificial insemination with husband's spermatozoa (AIH) whereby spermatozoa are deposited in the cervical canal or uterus (Allen *et al.* 1985), the placing of oocytes and spermatozoa into the uterus to allow fertilization to occur *in vivo* (Craft *et al.* 1982), and conventional in-vitro fertilization and embryo transfer (IVF-ET) in which fertilization occurs extracorporeally with subsequent transfer of embryos into the uterus (Edwards & Purdy 1982).

A procedure proving particularly successful is gamete intrafallopian transfer (GIFT), whereby oocytes and spermatozoa are transferred into the fallopian tubes. Since the first report (Asch *et al.* 1984), GIFT seems to give similar results at most centres using the technique (Guastella *et al.* 1985; Asch *et al.* 1986; Corson *et al.* 1986; Molloy *et al.* 1986; Nemiro *et al.* 1986; Yovich *et al* 1986) and pregnancy rates of the order of 30 per 100 treatment cycles can be achieved for normospermic couples (Asch 1986).

The present study describes the results of the GIFT programme at PIVET Medical Centre and the principal aims were to determine: the pregnancy outcomes in relation to the underlying infertility aetiology; the effect of transferring different numbers of oocytes on the pregnancy rates; whether pregnancy rates are improved by hyperstimulation as gauged by the number of oocytes collected; the outcome of pregnancies achieved following GIFT; and the relation

PIVET Medical Centre, 166–168 Cambridge Street, Leederville, Perth, Western Australia 6007
JOHN L. YOVICH
PHILLIP L. MATSON
DAVID G. BLACKLEDGE
SIMON R TURNER
PETER A. RICHARDSON
JEANNE M. YOVICH
W ROHINI EDIRISINGHE

Correspondence. Dr John L. Yovich

between the number of oocytes transferred and the frequency of multiple pregnancies.

Subjects and methods

The study was undertaken at the PIVET Medical Centre and was based on the first 207 GIFT treatment cycles in 73 couples without any recognizable male factors. All male partners were normospermic, the ejaculates containing $\geq 12 \times 10^6$ motile spermatozoa/ml (Yovich *et al.* 1985*a*). Couples with antispermatozoal antibodies either in male semen or in female serum were not included. Each woman had at least one fallopian tube shown to be patent and mobile at laparoscopy. Underlying tubal damage was known to be present in 22 women, a further 13 women had endometriosis graded according to classification published by the American Fertility Society (1985), 16 had a suspected cervical factor because of negative postcoital tests (Matson *et al.* 1986) and 22 women had completely unexplained infertility.

All women in this study had follicular growth stimulated by clomiphene citrate (Clomid, Merrell-Dow Pharmaceuticals, Inc.), human menopausal gonadotrophin (hMG; Pergonal, Serono) or a combination of both. The response to treatment was monitored daily from day 2 of the menstrual cycle by radioimmunoassay of serum oestradiol-17β, progesterone and luteinizing hormone (LH) levels, and from day 8 of the cycle using ultrasound. Ovulation was triggered by the occurrence of an endogenous LH surge or the administration of 10 000 i.u. human chorionic gonadotrophin (hCG; Primogonyl, Schering) at an appropriate time (Yovich *et al.* 1985*b*) and oocytes were collected approximately 35 h later via laparoscopy or an ultrasonically guided needle.

Husbands produced a semen sample by masturbation 2 h before the oocyte collection. Motile spermatozoa were then isolated using the swim-up technique employed in the IVF programme (Yovich & Stanger 1984). The final suspension of motile spermatozoa was adjusted to 2000/μl. The culture medium used was human tubal fluid (HTF) medium (Quinn *et al.* 1985) supplemented with 20% heat-inactivated serum.

Once oocytes had been collected, the gametes were transferred to the fallopian tube at laparoscopy. The GIFT catheter was a 50-cm-long 16-gauge end-hole Teflon catheter (William Cooke, Australia). The catheter was then loaded with: (a) HTF medium with 20% serum to fill the dead space; (b) 5 μl air; (c) 25 μl of medium with oocytes; (d) 5 μl air; (e) 50 μl of spermatozoal suspension; (f) 5 μl air.

The fallopian tube was then catheterized (Molloy *et al.* 1986) and the gametes were transferred. Patients were allowed to go home after they recovered from anaesthesia and were free to carry on normal activities, including work and sexual relations. Pregnancies were diagnosed by an elevated serum β-hCG level on or after day 16 of the luteal phase and eventually categorized according to the criteria published by Yovich & Matson (1988) as a biochemical pregnancy (falling hormone levels and no detectable gestational sac on ultrasound), blighted ovum (gestational sac at 7 weeks without a clear fetus and fetal heart action), miscarriage (fetal loss after ultrasound detection of fetal heart movement) and late pregnancy loss (fetal or neonatal death after 20 weeks gestation).

The χ^2-test was applied for statistical analysis in contingency tables.

Results

The pregnancy rates achieved after GIFT were similar in the four categories of infertility treated (Table 1), the overall rate was 24·2% (50 in 207 cycles). However, the pregnancy rates were markedly influenced by the number of oocytes transferred into the fallopian tubes ($\chi^2 = 9{\cdot}37$, df $= 3$, $P<0{\cdot}025$). A comparison of individual groups using 2 × 2 contingency tables showed that the pregnancy rates were significantly lower in cycles when only one (2/21; $\chi^2 = 4{\cdot}10$, $P<0{\cdot}05$) or two (2/29; $\chi^2 = 6{\cdot}99$, $P<0{\cdot}01$) oocytes were transferred than when four oocytes were transferred (36/116). The number of pregnancies achieved in women in whom ovulation was triggered by an endogenous LH surge was particularly low when three or fewer oocytes were replaced (one pregnancy in 27 cycles) although the numbers are too small to allow reliable statistical analysis.

Among the women who had four oocytes transferred, the pregnancy rates did not differ between those from whom more than four oocytes were collected (26/87; 29·9%) and those with only four oocytes collected (10/29, 34·5%; $\chi^2 = 0{\cdot}22$).

The pregnancy outcome achieved after GIFT is given in Table 4. Of the 50 pregnancies achieved, 28 (56%) continued to delivery

Table 1. Pregnancy rates achieved after GIFT

	No. women	No. cycles	Pregnancies	Pregnancy rate/cycle
Tubal damage:				24·2%
Previous tubal surgery	13	37	10	
PID adhesions	9	25	5	
Endometriosis:				26·5%
Stage I	6	16	5	
Stage II	4	13	2	
Stage III	2	4	1	
Stage IV	1	1	1	
Cervical factor	16	39	10	25·6%
Unexplained	22	72	16	22·2%
Totals	73	207	50	24·2%

PID, Presumptive diagnosis of previous pelvic inflammatory disease.
Endometriosis classified according to American Fertility Society (1985) classification.

Table 2. Pregnancy rates according to the number of oocytes transferred

Ovulatory trigger	No oocytes transferred								Total	
	1		2		3		4			
LH surge	0/8		0/5		1/14		9/26		10/53	(18·9%)
hCG	2/13		2/24		9/27		27/90		40/154	(26·0%)
Total	2/21	(9·5%)*	2/29	(6·9%)*	10/41	(24·4%)	36/116	(31·0%)	50/207	(24·2%)

$^*P<0{\cdot}05$ compared with four oocytes transferred.

beyond 20 weeks. Two twin pregnancies ended in miscarriage at 12 and 14 weeks gestation and one woman in whom eight sacs and seven fetal hearts were detected miscarried at 18 weeks. This patient had four oocytes transferred. Four fetuses were terminated selectively by ultrasound-guided needling at 9 weeks (Mulcahy *et al.* 1984) but the remaining triplet pregnancy ended in miscarriage in the 18th week. We were unable to determine if the eight sacs were derived from duplication of the four oocytes or whether further spontaneous ovulation occurred after the GIFT procedure. Late pregnancy loss occurred in two twin pregnancies with fetal death at 23 and 24 weeks respectively, and in one singleton pregnancy at 24 weeks. Four ectopic pregnancies occurred in women with a history of surgery for tubal disease (4/37; 10·8%), suggesting that this group of patients is at particular risk.

The frequency of multiple pregnancies in relation to the number of oocytes transferred is shown in Table 5. The number of gestational sacs with fetal heart beats was recorded on the first obstetric ultrasound echogram at 7 weeks, and therefore includes the miscarriages and late pregnancy losses mentioned above. There is a clear trend in the frequency of multiple gestational sacs with the transfer of increasing numbers of oocytes. Specifically, 100% (3/3) triplet pregnancies resulted from the transfer of four oocytes; 75% (6/8) and 25% (2/8) twin pregnancies were diagnosed in women who had four and three oocytes transferred.

Discussion

Experience of IVF-ET suggests that the pregnancy rate increases when the number of embryos replaced is increased (Osborn & Moor 1985). The present study has demonstrated a similar phenomenon with GIFT when increasing numbers of oocytes are transferred, with rates being maximal when three or four oocytes are replaced. This pattern is parallel to that described recently from a multi-centre study (Asch 1986) in which pregnancy rates of 4%, 19%, 44% and 41% were obtained from a total series of 800 cases when 1, 2, 3 or 4 oocytes were transferred. Such a trend is not always seen, and Nemiro & McGaughey (1986) found no association between the pregnancy rate and the number of oocytes replaced at GIFT. They obtained pregnancy rates of 40%, 29%, 21% and 46% after the transfer of 1, 2, 3 and 4

Table 3. Pregnancy rates after transfer of four oocytes according to the number of oocytes collected

Ovulatory trigger	No. oocytes collected 4	5	6	7	8	9	10	≥10	Total
LH surge	2/10	2/7	1/3	2/4	1/1	—	—	1/1	9/26 (34·6%)
hCG	8/19	4/17	5/18	5/11	1/4	2/9	0/4	2/8	28/90 (30·0%)
Total	10/29 (34·5%)	6/24 (25·0%)	6/21 (28·6%)	7/15 (46·7%)	2/5 (40·0%)	2/9 (22·2%)	0/4 (—)	3/9 (33·3%)	36/116 (31·0%)

oocytes. It is also apparent from the present study that the pregnancy rates, when three or fewer oocytes were transferred, were reduced when ovulation was triggered by an endogenous LH surge. This may be due to the immaturity of the transferred oocytes because of the difficulty in determining accurately the time of the onset of the LH surge by the analysis of daily blood samples. No difference in fertilization or pregnancy rates has been found in our IVF programme between oocytes collected following an LH surge or hCG injection (unpublished data), although this may be explained by the delayed insemination of oocytes (Trounson *et al.* 1982) as routinely practised, allowing any immature oocytes to complete the maturational process (Osborn & Moor 1985) in culture. The possibility of performing IVF-ET or pronuclear stage tubal transfer (PROST) (Yovich *et al.* 1987) in those women with ≤3 oocytes and ovulation triggered by an endogenous LH surge requires further consideration. If maturity of the oocytes is a problem, then their pre-incubation for IVF-ET or PROST should be beneficial.

Table 4. Pregnancy outcome in patients who conceived after GIFT

Pregnancy outcome	No. pregnancies	%
Delivered at ≥20 weeks	28	(56%)
Biochemical	6	(12%)
Blighted ovum	6	(12%)
Miscarriage	3	(6%)
Ectopic	4	(8%)
Late pregnancy loss	3	(6%)
Total	50	(100%)

Table 5. Frequency of multiple pregnancies diagnosed at 7 weeks by ultrasound, according to the number of oocytes transferred

Pregnancy	No. oocytes transferred 1	2	3	4	Total
Singleton	—	2	6	14	22
Twins	—	—	2	6	8
Triplets	—	—	—	3	3
>3 sacs	—	—	—	1	1
Total	—	2	8	24	34

The present study has shown that the stimulation of follicular growth to the extent that supernumerary oocytes are recovered does not increase the chance of pregnancy in that particular treatment cycle. This is of interest because studies on IVF-ET have demonstrated that higher serum progesterone concentrations in the early luteal phase are associated with the establishment of pregnancy (Garcia *et al.* 1984; Yovich *et al.* 1985*c*). This, coupled with the observation that the aspiration of follicles removes granulosa cells and disrupts progesterone secretion in some patients (Garcia *et al.* 1981; Frydman *et al.* 1982), might suggest that increased numbers of follicles would help maintain luteal phase progesterone concentrations and confer some benefit. Whilst not affecting the pregnancy rate per treatment cycle, the fertilization *in vitro* of supernumerary oocytes and the subsequent cryopreservation of embryos can increase the chance of pregnancy per oocyte collection by enabling women to have the transfer of a thawed embryo or embryos at a later date (Mohr *et al.* 1985).

The present series does not include male factor infertility. We did explore this area and found a need to develop a modified GIFT technique to achieve pregnancies (Matson *et al.* 1987). We also avoided GIFT in cases where either partner had antispermatozoal antibodies because one of the limitations of GIFT is that the procedure does not allow the confirmation of fertilization in couples who do not conceive. This may eventually become possible when the platelet agglutinating factor (PAF) test is fully developed and becomes available (O'Neill *et al.*

1987). The use of supernumerary oocytes as an in-vitro test of fertilization is not useful as a determinant of fertilization *in vivo,* since pregnancies can be achieved when the supernumerary oocytes fail to fertilize (Matson *et al.* 1987). In the groups of patients treated here (unexplained infertility, non-occlusive tubal damage, endometriosis and cervical factor) the chance of pregnancy was equivalent and the technique of GIFT appears equally indicated. However, those cases with a severe male factor, antispermatozoal antibodies and a poor history with repeated failures to conceive in the GIFT programme are best treated by the PROST method (Yovich & Matson 1988). At the PIVET Medical Centre, the technique of IVF-ET is now reserved for cases of irremediable tubal occlusion or in non-occlusive tubal disease where neither fallopian tube can be mobilized satisfactorily for successful cannulation in the GIFT and PROST procedures. Of course, it can be argued that many patients with patent fallopian tubes will conceive and do not need IVF, GIFT or PROST treatments. But the spontaneous rate of conception in such patients on the waiting list is of the order of only 5% per annum (unpublished observations). Clearly GIFT treatment enhances fertility, such that if each case could be treated up to three times per annum, more than 70% would have conceived. It may also be considered that only the transfer of oocytes to the fallopian tubes is necessary in those patients who demonstrate satisfactory postcoital tests. This may well be the case and requires further study as relevant data were not generated in this series.

There was a clear association between the frequency of multiple pregnancies and the increasing number of oocytes transferred, in agreement with Nemiro & McGaughey (1986) who reported more triplet and quadruplet pregnancies when four oocytes were transferred. In view of the similar pregnancy rate in this study and elsewhere (Asch 1986) when three or four oocytes are replaced, consideration should be given to limiting the number of oocytes transferred to three. This may also have the benefit of reducing the frequency of multiple pregnancies. One of our patients had seven gestational sacs with fetal pulse activity detected following the transfer of only four oocytes. Although the precise reason for this remains unknown, possibilities include multiple monozygotic twins or delayed ovulation from a secondary cohort of follicles.

The high ectopic pregnancy rate (6%) is not greater than that observed in subfertile patients conceiving after other treatments, including ovarian stimulation, intrauterine insemination with husband's washed sperm, IVF or after reconstructive tubal microsurgery (Yovich & Matson 1988). All cases in this series occurred in patients with known non-occlusive tubal diseases but the rate (4/98; 4·1%) is not excessive for this group and even the rate of 10·8% in women who had previous reconstructive surgery should not preclude GIFT as a treatment option for those who fail to conceive readily after tubal repair where at least one tube remains patent.

References

Allen, N C., Herbert, C M., Maxson, W S , Rogers, B. J., Diamond, M. P. & Wentz, A C. (1985) Intrauterine insemination: a critical review. *Fertil Steril* **44,** 569-580.

American Fertility Society (1985) Revised American Fertility Society classification of endometriosis· 1985. *Fertil Steril* **43,** 351-352.

Asch, R. (1986) Results from multi-centre studies Presented at the XII World Congress on Fertility & Sterility, October 26–31, Singapore.

Asch, R. H., Ellsworth, L. R. & Balmaceda, J P (1984) Pregnancy following translaparoscopic gamete intrafallopian transfer (GIFT). *Lancet* **ii,** 1034.

Asch, R. H., Balmaceda, J. P., Ellsworth, L. R. & Wong, P C (1986) Preliminary experiences with gamete intra-fallopian transfer (GIFT). *Fertil Steril* **45,** 366-371.

Corson, S L., Batzer, F., Eisenburg, E., English, M E , White, S. M., Laberge, Y. & Go, K J. (1986) Early experience with the GIFT procedure. *J Reprod Med* **31,** 219-223.

Craft, I., McLeod, F , Green, S , Djahabakhch, O., Bernard, A & Twigg, H. (1982) Human pregnancy following oocyte and sperm transfer to the uterus. *Lancet* **i,** 1031.

Edwards, R. G. & Purdy, J. M. (1982) *Human Conception In-Vitro* Academic Press Inc , London.

Frydman, R., Testart, J , Giacomini, P , Imbert, M. C , Martin, E. & Nahari, K. (1982) Hormonal and histological study of the luteal phase in women following aspiration of the preovulatory follicle *Fertil Steril* **38,** 312-317

Garcia, J., Jones, G. S., Acosta, A. A. & Wright, G L. (1981) Corpus luteum function after follicle aspiration for oocyte retrieval. *Fertil Steril* **36,** 565-572.

Garcia, J. E , Acosta, A A., Hsiu, J. G. & Jones, H.

W. Jr (1984) Advanced endometrial maturation after ovulation induction with human menopausal gonadotrophin/human chorionic gonadotrophin for in vitro fertilization. *Fertil Steril* **41**, 31-35.

Guastella, G., Comparetto, G., Gollo, D., Palemo, R., Venezia, R , Cefalu, E., Cinmma. R. & Salerno, P. (1985) Gamete intrafallopian transfer (GIFT): a new technique for the treatment of unexplained infertility. *Acta Eur Fertil* **16**, 311-316.

Matson, P L., Tuvik, A. I , O'Halloran, F. & Yovich, J. L. (1986) The value of the PCT in predicting the fertilization of human oocytes. *J In Vitro Fert Embryo Transfer* **3**, 110-113.

Matson, P. L , Yovich, J M , Bootsma, B D., Spittle, J W. & Yovich, J. L. (1987) The in-vitro fertilization of supernumerary oocytes in a gamete intrafallopian transfer (GIFT) program *Fertil Steril* **47**, 802-806.

Mohr, L., Trounson, A. & Freeman, L. (1985) Deep-freezing and transfer of human embryos. *J In Vitro Fert Embryo Transfer* **2**, 1-10.

Molloy, D , Speirs, A. L., duPlessis, Y., Gellert, S., Bourne, H. & Johnston, W. I H. (1986) The establishment of a successful programme of gamete intra-fallopian transfer (GIFT): preliminary results. *Aust NZ J Obstet Gynaecol* **26**, 206-209.

Mulcahy, M. T , Roberman, B. & Reid, S. E. (1984) Chorion biopsy, cytogenetic diagnosis, and selective termination in a twin pregnancy at risk of haemophilia *Lancet* **ii**, 866-867

Nemiro, J S. & McGaughey, R. W. (1986) An alternative to in-vitro fertilization-embryo transfer: the successful transfer of human oocytes and spermatozoa to the distal oviduct. *Fertil Steril* **46**, 644-652.

O'Neill, C., Gidley-Baird, A. A., Pike, I L. & Saunders, D M (1987) Use of a bioassay for embryo-derived platelet-activating factor as a means of assessing quality and pregnancy potential of human embryos. *Fertil Steril* **47**, 969-975.

Osborn, J C & Moor, R. M. (1985) Oocyte maturation and developmental competence. In *In Vitro Fertilization and Donor Insemination*. Proceedings of 12th Study Group of the Royal College of Obstetricians and Gynaecologists (Thompson, W., Joyce, D. N. & Newton, J R., eds), RCOG, London, pp. 101-114

Quinn, P., Kerin, J. F. & Warner, G. M. (1985) Improved pregnancy rates in human in vitro fertilization with the use of a medium based on the composition of human tubal fluid. *Fertil Steril* **44**, 493-498.

Trounson, A. O., Mohr, L. R., Wood, C. & Leeton, J. F. (1982) Effect of delayed insemination on in-vitro fertilization, culture and transfer of human embryos. *J Reprod Fertil* **64**, 285-294.

Yovich, J. L. & Matson, P. L. (1988) Early pregnancy wastage following gamete manipulation. *Br J Obstet Gynaecol* **95**, (in press).

Yovich, J. L. & Stanger, J. D. (1984) Limitations of in-vitro fertilization from males with severe oligospermia. *J In Vitro Fert Embryo Transfer* **1**, 172-179.

Yovich, J. L., Stanger, J. D. & Yovich, J. M. (1985*a*) Management of oligospermic infertility by in-vitro fertilization. *Ann NY Acad Sci* **442**, 276-286.

Yovich, J L., Stanger, J. D., Yovich, J. M. & Tuvik, A I. (1985*b*) Hormonal profiles in the follicular phase, luteal phase and first trimester of pregnancy. *Br J Obstet Gynaecol* **92**, 374-384.

Yovich, J L , McColm, S C , Yovich, J. M. & Matson, P. L. (1985c) Early luteal serum progesterone concentrations are higher in pregnancy cycles *Fertil Steril* **44**, 185-189.

Yovich, J. L., Matson, P L , Turner, S R , Richardson, P & Yovich, J. M. (1986) Limitation of gamete intrafallopian transfer in the treatment of male infertility. *Med J Aust* **144**, 444.

Yovich, J. L., Blackledge, D. G., Richardson, P A., Matson, P. L., Turner, S R. & Draper, R (1987) Pregnancies following pronuclear stage tubal transfer (PROST). *Fertil Steril* **48**, 851-857.

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Bacteriological contamination during laparoscopy with dye injection

R. J. D. PYPER, ZERIN AHMET, ELIZABETH T. HOUANG

Summary. Peritoneal contamination with bacteria during the laparoscopy and dye procedure was studied in 38 subfertile women by culturing samples of peritoneal fluid, aspirated before, and after, injection of dye solution. Bacteria were carried with the dye into a previously sterile peritoneal cavity in 34 women (90%). These vaginal organisms were present in low concentrations, not exceeding 10^5 organisms/ml. These findings explain the low incidence of acute salpingitis after tubal patency tests, but the selective use of antibiotic prophylaxis is recommended.

The patency of fallopian tubes may be investigated by hysterosalpingography (HSG), or by a laparoscopy and dye procedure. The latter has become more popular, because it also allows diagnosis of peritubal and ovarian pathology.

In both procedures, a sterile aqueous solution is injected into the uterine cavity via a cannula in the endocervical canal. From a bacteriological point of view, the procedures are similar. Vaginal organisms may be carried into the fallopian tubes, causing salpingitis in a few instances and reducing the fertility of the couple.

The aim of this study was to determine the prevalence and nature of bacterial contamination occurring in the peritoneal cavity as a result of transcervical injection of dye during elective laparoscopy

Patients and methods

The study included 38 subfertile patients who were investigated by laparoscopy. They went home within 24 h and were seen again 6 weeks later. Instructions were given to contact the hospital should any symptoms arise.

Laparoscopy was performed in the usual manner. Chlorhexidine solution, 0·5% in 70% alcohol, was used to clean the abdomen, and the laparoscope was introduced after subumbilical insufflation through a Verres needle. The same needle was inserted through a suprapubic incision and the first sample of peritoneal fluid was aspirated from the recto-vaginal pouch An assistant had cleansed the vagina with a 0·05% aqueous solution of chlorhexidine. The cervix was grasped with a volsellum forceps, and a Spackman cannula was introduced into the cervical canal. A sterile aqueous solution of indigo-carmine dye was then injected into the uterine cavity. A second sample of peritoneal fluid was aspirated, after spill of dye from one or both tubes was seen. If no dye appeared, the patient was excluded from the study.

Three bacteriological methods were used to examine the peritoneal fluid.

Qualitative bacteriology

The frequency of bacterial contamination was assessed in the first 12 patients. Samples of aspirated fluid, obtained before and after the injection of dye, were injected into a pair of culture bottles containing either digest broth with 0·1%

Departments of Gynaecology and Microbiology, Chelsea Hospital for Women, Dovehouse Street, London SW3
R J D PYPER
ZERIN AHMET
ELIZABETH T. HOUANG

Correspondence R J. D. Pyper, Senior Registrar, Department of Gynaecology, St Bartholomew's Hospital, West Smithfield, London EC1A 7BE

glucose and liquid (Southern Group) or fastidious anaerobic broth with thymidine (Lab M). The bottles were incubated at 37°C, examined daily, and routinely subcultured on the 5th and 10th days or whenever the culture broth became turbid. Aerobic subculture was achieved with Columbia agar plates (Oxoid) with 5% horse blood, incubated in 7% CO_2 for 3 days at 35°C; and anaerobic subculture was performed with Wilkins and Chalgren agar plates with 7% horse blood, using an anerobic incubator (10% CO_2 5% H_2, 85% N_2) for 7 days. The bacterial isolates were identified in the usual way.

Quantitative bacteriology

Aspirated fluid was immediately transported to the laboratory in a sterile container and processed within 30 min. Two methods were used to quantify the bacteria.

Pour-plate method. For the next 16 patients the aspirated fluid samples were measured volumetrically and vortexed. Each sample was divided into two and each half was added to a bottle containing 100 ml of molten Wilkins and Chalgren agar. The contents of each bottle were thoroughly mixed and poured into 27-cm Petri dishes. The agar was allowed to set and then incubated. One plate was incubated aerobically in the CO_2 incubator for 3 days and the other in the anaerobic cabinet for 7 days. The concentration of organisms/ml of aspirate was calculated from the number of colonies in each plate and the bacterial isolates were identified.

Spread-plate method. In the remaining 10 patients 0·5 ml of aspirated fluid was inoculated onto a Wilkins and Chalgren agar plate with 5% horse blood for anaerobic incubation. The same amount of fluid was used to inoculate a Columbia horse blood agar plate, a McConkey plate, and a Columbia human blood agar plate with nalidixic acid (30 mg/l), gentamicin (4 mg/l) and amphotericin (4 mg/l). These three plates were incubated in the CO_2 incubator The colonies were counted and identified

Results

Of the 38 patients 24 complained of primary infertility whereas the remainder had secondary infertility. Both fallopian tubes were patent in 24 women, and 14 had unilateral spill only. The pelvic organs appeared entirely normal in 17 women. Evidence of previous tubal infection or surgery was found in 12 women, endometriosis in seven and other conditions in two women.

All cultures of the pre-injection peritoneal fluid from the qualitative study of the first 12 patients yielded no growth. Table 1 shows the frequency of isolation of different bacterial species after dye injection by the three methods. Sterile culture was obtained in two patients by each of the quantitative methods. The overall positivity rate of the three methods was 90%. Six cultures yielded only *Staphylococcus epidermidis* or diphtheroids. Organisms of definite vaginal origin were cultured in 28 patients (74%). The more fastidious species such as *Gardnerella vaginalis* and anaerobic cocci were isolated only by the spread-plate method. There was, however, no statistically significant difference in the number of species isolated by the three methods (Mann–Whitney *U*-test).

There was no significant difference in the positivity rate or the number of species isolated between patients suffering from primary or secondary infertility, with both or only one tube patent, or with different laparoscopic findings.

Table 2 shows the concentrations of bacteria isolated by the two quantitative methods. The bacterial concentrations most frequently recovered were between 10 and 100 organisms/ml, although concentrations of between 10^4 and 10^5 were found on four occasions.

Eight patients were mildly pyrexial (37–38°C) in the postoperative period, but all were afebrile on discharge. No patient subsequently complained of pelvic pain or vaginal discharge

Discussion

None of our patients developed a clinical infection after laparoscopy with dye injection. The number of patients studied is, however, too small to determine the frequency of postoperative infection, which, so far, has not been reported in the literature

In contrast, the frequency of postoperative pelvic inflammatory disease (PID) after hysterosalpingography (HSG) has been reported to be between 0·3% and 3·1%. Stumpf & March (1980) reviewed a series of 448 women undergoing HSG for a variety of indications, and noted that PID followed in 14 patients. The latter were all found to have had unilateral or bilateral hydrosalpinges They considered the

Table 1. The frequency of major bacterial species isolated from the peritoneal fluid after injection of dye by the three bacteriological methods

Bacteria	Bacteriological method			Total
	Qualitative	Pour-plate	Spread-plate	
Lactobacillus spp	4	9	7	20
Anaerobic species*	5	3	7	15
Gardnerella vaginalis	0	0	5	5
Streptococci†	5	0	2	7
Diphtheroids	2	6	6	14
Staphylococcus epidermidis	5	9	4	18
Other species	3	4	1	8
Average number of species per patient	2	1·94	3·2	2·3
Number of patients studied	12	16	10	38

* Anaerobes: including *Bacteroides* spp , anaerobic Gram-positive cocci and rods

† Streptococci: including beta-haemolytic groups D and B, microaerophilic and alpha-haemolytic species

Table 2. The concentrations of major bacterial species found in the peritoneal fluid after injection of dye by the two quantitative methods used in 26 patients

Bacteria	Total number of positive cultures with bacterial concentrations (colony forming units/ml) at				
	≤ 10	>10–10^2	$>10^2$–10^3	$>10^3$–10^4	$>10^4$–10^5
Lactobacillus spp.	1	7	3	4	1
Anaerobic species*	4	4		1	1
Gardnerella vaginalis		3		1	1
Streptococci†	2				
Diphtheroids	4	7	1	1	1
Staphylococcus epidermidis	9	4			
Total	20	25	4	7	4

* Anaerobes: including *Bacteroides* spp , anaerobic Gram-positive cocci and rods

† Streptococci: including beta-haemolytic groups D and B, non-haemolytic and alpha-haemolytic spp

risk factors to be a history of previous pelvic infection or surgery for infection, a history of infertility and a record of a previous adnexal mass or tenderness. PID was rare if only one factor was present; and it was not found among the women with normal tubes. However, if three or more factors were present, HSG caused acute salpingitis in 57%. They also claimed not to have seen a single instance of PID after laparoscopy with dye injection despite 'extensive use' of the technique in the same population.

We used the well-established technique of blood cultures to determine the qualitative frequency of contamination. In the quantitative study, the small volume of fluid obtained and the extra laboratory workload precluded us from examining these specimens by both methods concurrently. The spread-plate method included horse blood, as a supplement, and antibiotics for selective culture, factors likely to result in a greater chance of isolation of the more fastidious vaginal species It is therefore recommended for future studies.

The source of the bacterial contamination demonstrated in our study is the lower genital tract, as the peritoneal fluid samples were all sterile before the injection of dye. The samples were not cultured for the presence of mycoplasmas, viruses or chlamydia, but it is likely that these organisms would also be introduced into the peritoneum if they were present in the endocervical flora. The role of chlamydia in PID has been recognized (Mardh *et al.* 1977). The overall positivity rate in the samples after injection of dye was 90%. Organisms, such as *S. epidermidis* and corynebacteria may be found on the skin, as well as in the vagina; whereas others, such as lactobacilli and *G. vaginalis*, are considered to be of vaginal origin (Insenberg & D'Amato 1985). Thus, the positivity rate for vaginal organisms, other than *S. epidermidis* and corynebacteria, was 74% (28/38).

In the pathogenesis of infection, the number and virulence of microbes, and the host resistance, at both local and systemic levels, are important factors. Gilmore (1981) stated that the frequency of postoperative sepsis has been shown to be related to the number of organisms present in the peritoneal cavity and stated that an inoculum of less than 10^5 organisms/ml was unlikely to cause sepsis. Our results show that the number of organisms contaminating the peritoneal cavity was usually small, 23/32 of the isolates were found to be less than 10^3 per ml. This may explain why postoperative infection is not a common occurrence after HSG or laparoscopy and dye injection, despite the high frequency of peritoneal contamination by vaginal flora.

Stumpf & March (1980) suggested that the infection after HSG was due to an acute exacerbation of a chronic pelvic infection. We believe such an infection is not likely to be due to reactivation. Our study shows that transcervical injection of fluid can introduce anaerobes and other microbes into the peritoneum. However, patent fallopian tubes with healthy ciliated epithelium may be resistant to the low concentration of bacteria introduced during the injection of dye. If a hydrosalpinx is present, the local resistance may be much reduced. Here the bacterial inoculum is likely to be instilled into static serous fluid within a fibrous walled cyst with no ciliated epithelium. The blood supply of the wall may also be reduced which may create conditions favourable to the multiplication of bacteria and lead to the development of clinical infection.

To prevent infection after HSG, prophylactic antibiotics have been given to patients considered to be at risk, but the results have been variable. Stumpf & March (1980) failed to prevent infection in 9 of 14 patients treated with ampicillin for 2 days before and after the procedure; whereas Pittaway *et al.* (1983) successfully prevented infection in 56 patients, by treating them with prophylactic doxycycline, after dilated tubes had been found on HSG.

A large prospective study is necessary to determine the prevalence of PID, and its risk factors, after laparoscopy with dye injection. The procedure is similar to HSG, yet there may be important differences. For example, some surgeons may not proceed with the dye injection if hydrosalpinges are seen during laparoscopy. In our study, we excluded patients with bilateral tubal occlusion. As HSG is often performed in conscious patients, the cervix and vagina may be less thoroughly disinfected than in patients undergoing laparoscopy under general anaesthesia. It is unclear whether these factors would affect transcervical contamination and the clinical sequelae.

Nevertheless, in view of our findings, we make the following suggestions to prevent the development of PID following laparoscopy with dye injection. First, dye should not be injected if bilateral hydrosalpinges are clearly seen, as tuboplasty is not indicated. Second, if a unilateral hydrosalpinx is seen and dye is injected to elucidate the state of the other tube, antibiotic prophylaxis should be given as soon as possible. The best choice of treatment is not certain, although a regimen of doxycycline, 100 mg twice daily for 5 days, was shown to be effective by Pittaway *et al.* (1983). If the tubes appear healthy and patent, antibiotic prophylaxis is not indicated.

In conclusion, low concentrations of vaginal organisms were cultured from fluid in the rectovaginal pouch, after transcervical injection of dye in 74% of cases. No case of PID was found in our series, involving only a small number of patients, but this complication is more common in patients with hydrosalpinges. It is, therefore, suggested that infection may be prevented, by avoiding injection of dye into hydrosalpinges, and giving doxycycline postoperatively if this occurs.

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References

Gilmore, O. J. A. (1981) Wound healing: the problem of infection. *Curr Surg Pract (RCS Eng* 1981) **3,** 95-108.

Isenberg, H. D. & D'Amato, R. F. (1985) Indigenous and pathogenic micro-organisms of humans. In *Manual of Clinical Microbiology*, Washington DC, pp 24-25

Mardh, P.-A , Ripa, K. T., Svensson, L. & Westrom, L. (1977) *Chlamydia trachomatis* infection in patients with acute salpingitis. *N Engl J Med* **296,** 1377-1379.

Pittaway, D. E., Winfield, A. C., Maxson, W., Daniell, J., Herbert, C. & Wentz, A C. (1983) Prevention of acute pelvic inflammatory disease after hysterosalpingography: efficacy of doxycycline prophylaxis. *Am J Obstet Gynecol* **147,** 623-626.

Stumpf, P. G. & March, C. M. (1980) Febrile morbidity following hysterosalpingography· identification of risk factors and recommendations for prophylaxis. *Fertil Steril* **33,** 487-492.

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Cervical dilatation by Lamicel before first trimester abortion: a clinical and experimental study

A. NORSTRÖM, I. BRYMAN, H.-A. HANSSON

Summary. Twenty women were treated with Lamicel tents for 4 h and 20 women for 16 h before vacuum aspiration in the first trimester of pregnancy. The shorter time of treatment was as effective as the longer time with respect to cervical softening and dilatation. In comparison with an untreated control group, Lamicel treatment was followed by an increased collagenolytic activity and increased sensitivity to prostaglandin E_2 of the cervical smooth muscle.

Mechanical dilatation of the cervical canal with tapered metal cylinders of increasing diameter is traumatic and can be associated with adverse short- and long-term effects (Hulka & Higgins 1961). The insertion of laminaria tents or other hydrogels or the local application of prostaglandins can soften and widen the cervical canal during pregnancy (Hale & Pion 1972; Karim 1975). During the last few years, Lamicel has been used to ripen the cervix before vacuum aspiration in the first trimester (Nicolaides *et al.* 1983). Lamicel is a synthetic polyvinyl alcohol polymer sponge, impregnated with 200 mg of magnesium sulphate and compressed to form a tapered cylindrical tent. The tent absorbs water and swells to four times its original size. In the present study the clinical effects of Lamicel application are correlated with cervical tissue changes.

Subjects and methods

Sixty women who were to have legal termination of their first pregnancy were recruited to the study. All gave their informed consent and the experimental design was approved by the local ethics committee. Twenty women (mean gestational age 10·5 weeks; mean age 20·7 years) were treated with Lamicel for 4 h (4-h group) and 20 women (mean gestational age 9·8 weeks; mean age 21·1 years) were treated with Lamicel for 16 h (16-h group) before abortion. Twenty primigravidae of corresponding age and gestation constituted a control group. Gestation was determined from the date of the last menstrual period, uterine size and ultrasonography.

One week before operation, culture specimens for isolation of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* were taken from the cervix. In the 4-h group the Lamicel was inserted on the morning of the day of operation and the women were kept supine until vacuum aspiration. In the 16-h group the tent was inserted in the afternoon the day before the operation and the women were ambulant until operation. After cleaning the vaginal vault with 0·5% chlorhexidine solution, a Lamicel tent (3 mm diameter, Vingmed Svenska AB, Jarfälla, Sweden) was inserted into the cervical canal with the tip of the tent just through the internal os. A small vaginal pack was inserted to ensure the Lamicel tent remained *in situ*. Discomfort (pain, nausea) or bleeding was recorded. The patients were given routine premedication and general anaesthesia. The pre-operative dilatation of the cervical canal was determined by the largest diameter of Hegar dilators that passed the internal os

University of Göteborg, The Sahlgren's Hospital, Göteborg, Sweden
Department of Obstetrics and Gynecology
A. NORSTROM
I. BRYMAN

Department of Histology
H.-A. HANSSON

Correspondence. Dr Anders Norstrom, Department of Obstetrics and Gynecology, The Sahlgren's Hospital, S-413 45 Goteborg, Sweden

without resistance. Details of the operation procedures including blood loss were recorded.

Before vacuum aspiration, cylinder-shaped specimens of cervical tissue (approx. 1·5×15 mm) were taken with the use of a biopsy needle (TruCut, Travenol, Deersfield, IL, USA) (Norström 1982). One piece of tissue was immediately fixed in buffered glutaraldehyde (Karnowsky 1965) and the remainder was transferred to chilled oxygenated Krebs-Ringer bicarbonate (KRB) buffer, pH 7·38.

Cervical specimens were incubated for 2 or 4 h in oxygenated KRB-buffer in the presence of ^{3}H proline (100 Ci/mmol, New England Nuclear Co., Boston, MA, USA). After incubation the tissue was rinsed in several baths of ice-chilled unlabelled buffer. The proteins were precipitated by immersion of the tissue in 12% (w/w) trichloro-acetic acid and lipids were extracted in two changes of chloroform:methanol (2:1, v/v). After determination of dry weight the tissue was dissolved in Soluene 350 (Packard Instrument Company, Downers Grove, IL, USA, 0·5 N quaternary ammonium hydroxide in toluene) (50°C; 12 h). Radioactivity was determined by liquid scintillation counting and expressed as ct/min per mg dry weight.

Cervical specimens from the 4-h group were homogenized in 0·05 M Tris-HCl buffer and the homogenates were centrifuged at 10 000 *g* for 1 h. Aliquots of the supernatant were removed for determination of hydrolytic activity against 2-4 dinitrophenyl-Pro-Glu-Gly-Ile-Ala-Gly-Glu-D-Arg-OH (DNP-peptide, The Protein Research Foundation, Osaka, Japan) (Masui *et al.* 1977). The pellets were dissolved and heated in 1 M NaOH and aliquots were taken for determination of protein (Lowry *et al.* 1951). Cervical specimens from the 16-h group were incubated for 4 h in medium M 199 with Earle's salts (pH 7·38, Gibco Ltd, UK) and serum albumin (2 mg/ml). After incubation the medium was dialysed against two changes of ice-chilled Tris-HCl buffer for 24 h, freeze dried and dissolved in buffer for measurements of hydrolytic activity against DNP-peptide.

Other strips of tissue were mounted in tissue chambers under superfusion with oxygenated KRB buffer (Bryman *et al.* 1984*a*). Muscle activity was registered isometrically under a passive tension of 5 mN. The end of the tissue strip was connected to a force transducer (Grass Model FT03). The sensitivity of the cervical smooth muscle to prostaglandin E_2 and noradrenaline was compared between those treated with Lamicel and the control group.

For electron microscopy the fixed tissue was further postfixed in osmium-tetroxide and dehydrated in increasing concentrations of ethanol before embedding in EPON. Ultrathin specimens were prepared with the use of a LKB-ultratome.

Statistics

The mean (SEM) values were calculated and the significance of difference between treated and control women was estimated using Student's *t*-test.

Results

The Lamicel tents were inserted easily and without any serious discomfort to the patients. Only three women in the 16-h group experienced mild and transient dysmenorrhea-like pain a few hours after insertion None experienced nausea or vomiting. At the time of the abortion all tents in the 4-h group were found in the cervical canal, whereas in three patients in the 16-h group the Lamicel tents were half in the vagina. All the tents were removed without difficulty. The mean dilatation of the cervix was 8·3 (SEM 0·27) mm in the 4-h group, 7·8 (SEM 0·42) mm in the 16-h group and 4·0 (SEM 0·30) mm in the control group. In both Lamicel-treated groups the additional dilatation to Hegar 9 or 11 was achieved with only slight resistance.

The Lamicel-treated patients required reduced amounts of anaesthetic agents because of the ease of cervical dilatation. There was an impression that the uterine cavity was evacuated more easily in treated women. Blood loss was not significantly different from that in controls One woman in the 16-h group underwent another aspiration 3 days after the primary operation because retained products were suspected but only blood clots were found within the uterine cavity. None of the 60 women had symptoms or signs of postoperative endometritis and all were healthy when examined 14 days after operation. The biopsy technique was not associated with any per- or postoperative complication.

The effects of Lamicel on cervical collagen were studied by measuring the incorporation of ^{3}H proline into cervical tissue as well as the hydrolytic activity against the synthetic oligopeptide DNP-peptide.

The incorporation of ^{3}H proline into cervical tissue after 1 h of incubation was significantly greater in Lamicel-treated women than in the control group, but after 2 h incubation the difference between the two groups was not statistically significant (Table 1). The Lamicel-induced cervical dilatation was associated with an increased collagenolytic activity. Thus, the hydrolytic activity against DNP-peptide was higher in tissue from patients treated with Lamicel for 4 h than in controls and the recovered enzyme activity in the media after incubation of cervical tissue from women in the 16-h group exceeded that of control tissue (Table 2).

Electron microscope examination of cervical tissue after Lamicel treatment supported the biochemical finding of increased collagen breakdown. The collagen fibrils appeared disrupted and disintegrated and the amount of ground substance appeared increased (Fig. 1).

The spontaneous smooth muscle contractile activity of strips of Lamicel-dilated cervices was similar to that of control tissue strips, the pattern of contractions being of a short duration, high frequency type (Fig. 2; see Bryman *et al.* 1984*a*). The response to noradrenaline was also similar to that of the controls, stimulation of contractile activity occurring at concentrations of 10^{-7}–10^{-6} M (Fig. 2; see Bryman *et al.* 1984*b*). PGE$_2$ inhibited spontaneous contractions at extremely low concentrations in strips from Lamicel-treated as well as control women. Inhibition of contractile activity was obtained in 56% of strips from Lamicel-treated patients compared with 38% of strips from control women (Bryman *et al.* 1984*a*).

Table 1. Incorporation of ^{3}H proline into cervical tissue from patients treated with Lamicel for 16 h and a control group

Duration of incubation	Radioactivity (ct/min per mg dry weight)	
	Lamicel group (n = 11)	Control group (n = 11)
1 h	2987 (205)*	2383 (221)
2 h	4358 (458)	4563 (481)

Significance of difference between the two groups
* $P<0{\cdot}05$

Table 2. Collagenolytic activity in cervical tissue from patients treated with Lamicel and a control group

Sample	Collagenolytic activity†	
	Lamicel group	Control group
Cervical tissue	159 (18·7)*** (n = 18)	83 (9·2) (n = 8)
Medium after 4-h incubation of cervical tissue	29 (3·6)* (n = 11)	19 (2·0) (n = 10)

† Measured as the hydrolytic activity to DNP peptide and expressed as means (SEM) of units/mg dry weight
Significance of difference between the two groups
* $P<0{\cdot}05$, *** $P<0{\cdot}001$

Discussion

From a clinical point of view Lamicel tents are easily handled and are effective in dilating the cervix before first trimester abortion. The tent is not too stiff and can be bent to fit the position of the cervix. The tapered end facilitates the insertion. The short 4-h period of application had several advantages: the patient had to attend the hospital only on the day of operation and could be more easily observed before operation. In addition, the dilatation was greater after 4 h (8·3 mm) than after 16 h (7·8 mm) of application which may be explained by the supine position of the patients in the former group. Postoperative infections were not observed among the 40 Lamicel-treated or 20 control patients, though the prevalence of postoperative infection was 2·2% among all patients undergoing abortion during the period of this study. The reduced resistance to the Hegar dilators may diminish the risk of cervical damage and the risk of transferring bacterial agents to the uterine cavity. A reduced frequency of postoperative endometritis has also been reported among patients having pre-operative treatment with Laminaria tents (Gold *et al.* 1980).

Proline is one of the predominant amino acids of the collagen molecule and is the natural precursor of collagen-specific hydroxyproline. Consequently, radiolabelled proline is widely used as a precursor in studies on collagen metabolism (Minor 1980). The measured radioactivity as related to tissue dry weight comprises several steps involved in protein metabolism: uptake of the amino acid, its incorporation into protein and further hydroxylation, breakdown of the molecule formed and the escape of breakdown products from the cell. Although it cannot be stated conclusively that the recovered radioac-

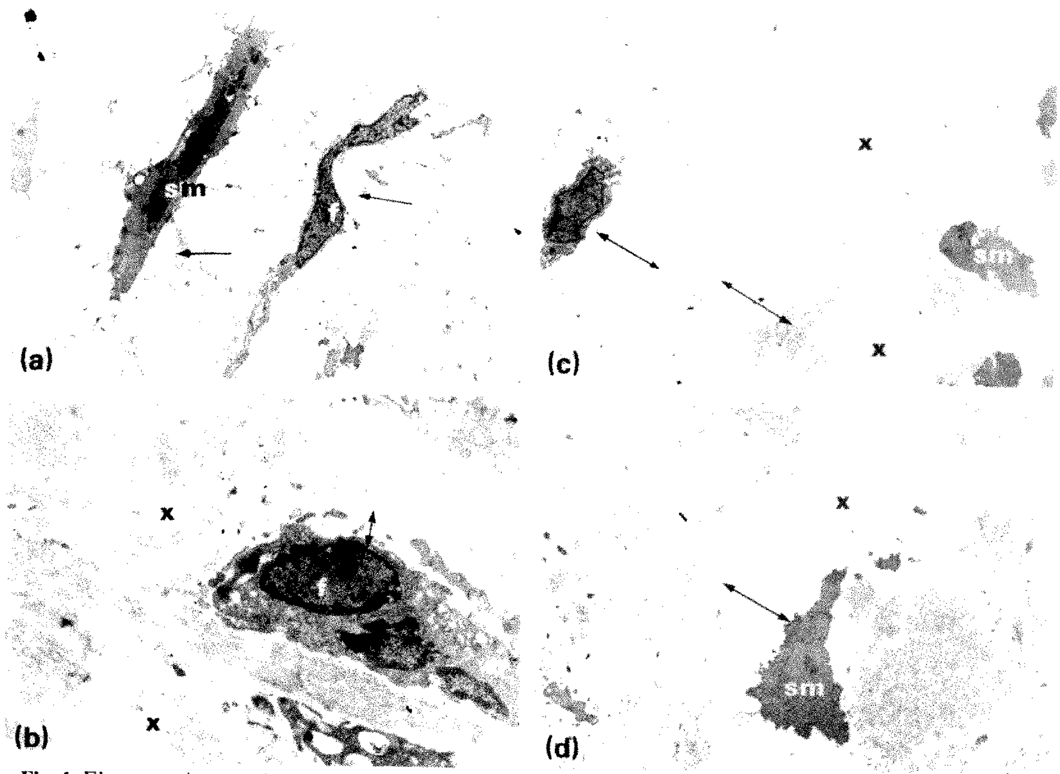

Fig. 1. Electron micrographs of cervical tissue from women in the first trimester of pregnancy. (a) Control group. Note the regular arrangement of intact collagen fibrils (arrows) in the close vicinity of fibroblasts (f) and smooth muscle cells (sm) (×2600); (b–d) Lamicel-treated groups: (b) 4-h group; (c, d) 16-h group. The collagen fibrils appear partly disintegrated (x) and are located at some distance from the fibroblast (f) (arrows) (×2600) (c); ×6500 (b, d).

tivity does represent newly formed collagen the observed difference between Lamicel-treated and control cervical tissue after incubation for 1 h indicates that the softening of cervix after Lamicel treatment is associated with altered collagen metabolism (increased turnover rate of newly synthesized collagenous proteins?). Such an interpretation is in line with previous studies

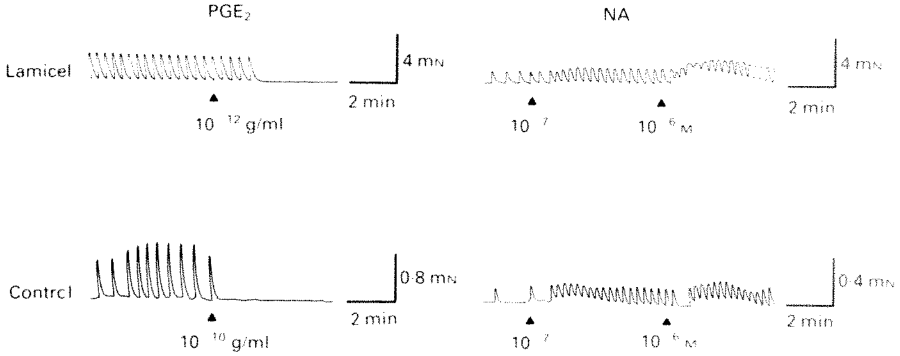

Fig. 2. Effects of prostaglandin E_2 (PGE_2) and noradrenaline (NA) on cervical contractile activity in the first trimester of pregnancy. Low concentrations of PGE_2 (10^{-12}g/ml) inhibited spontaneous contractions (56% inhibition in Lamicel-treated women and 38% inhibition in the control group). Noradrenaline stimulated contractile activity (increased frequency, amplitude and tonus) at the same concentrations (10^{-7}–10^{-6}M) in strips from control and Lamicel-treated women (right panel).

on the effects of endocervically administered PGE_2 gel on cervical connective tissue, demonstrating changes in the rate of incorporation of proline as well as glucosamine during cervical softening (Norström 1983).

The measurement of hydrolytic activity against the collagen-like DNP-peptide is an accepted method for estimating collagenase activity (Masui *et al.* 1977). This method was used to assess the production of collagenase both *in vivo* (4-h group) and *in vitro* (16-h group). It was obvious that the treatment with Lamicel was associated with increased collagenolytic activity in cervical tissue. These results are in agreement with those of other studies using the same DNP-peptide method for measurement of collagenolytic activity in human cervical tissue following ripening of the cervix by PGE_2 gels (Ekman *et al.* 1983). The biochemical evidence of augmented collagen breakdown was further supported by the disintegration and dissolution of collagen fibrils observed on electron microscopy. That picture is similar to that observed in cervical tissue in association with a spontaneous or PG-induced softening process (Junqueira *et al.* 1980; Uldbjerg *et al.* 1981).

Although the pattern of spontaneous muscle contractions did not differ between control and Lamicel-treated women, the sensitivity to PGE_2 increased slightly after treatment with Lamicel. This supports previous suggestions that cervical maturation is dependent on the adaptive response of both the connective tissue and the smooth muscle (Bryman *et al.* 1984*a,b*).

References

Bryman, I., Sahni, S., Norström, A. & Lindblom, B. (1984*a*) Influence of prostaglandin on contractility of the isolated human cervical muscle. *Obstet Gynecol* **63**, 280-284.

Bryman, I., Lindblom, B., Norström, A. & Sahni, S. (1984*b*) Adrenoceptor mechanisms in the regulation of contractile activity in the human cervix. *Obstet Gynecol* **64**, 363-367.

Ekman, G., Uldbjerg, N., Malmström, A. & Ulmsten, U. (1983) Isolated postpartum collagenolytic activity in cervical connective tissue from women treated with prostaglandin E_2. *Gynecol Obstet Invest* **16**, 292-298.

Gold, J., Schultz, K. F., Cates Jr, W. & Tyler Jr, C. W. (1980) The safety of Laminaria and rigid dilators for cervical dilation prior to suction curettage for first trimester abortion: A comparative analysis. In *Dilatation of the Uterine Cervix* (Naftolin, F. & Stubblesfield, P. G., eds), Raven Press, New York, pp. 363-370.

Hale, R. W. & Pion, R. J. (1972) Laminaria: An underutilized clinical adjunct. *Clin Obstet Gynecol* **15**, 829-850.

Hulka, J. F. & Higgins, G. (1961) Trauma to the internal cervical os during dilatation for diagnostic curettage. *Am J Obstet Gynecol* **113**, 442-448.

Junqueira, L. C. K., Zugaib, M., Montes, G. S., Toudo, O. M. S., Krisztan, R. M. & Shigihara, K. M. (1980) Morphologic and histochemical evidence for the occurrence of collagenolysis and for the role of neutrophilic polymorphonuclear leucocytes during cervical dilatation. *Am J Obstet Gynecol* **138**, 273-281.

Karim, S. M. M. (1975) *Prostaglandins and Reproduction*, MTP Press Ltd, Edinburgh, pp. 77-148.

Karnowsky, N. J. (1965) A formaldehyde-glytaraldehyde fixative of high osmoloarity for use in electron-microscopy. *J Cell Biol* **27**, 137A.

Lowry, O. H., Rosebrough, N. J., Farr, A. L. & Randall, R. J. (1951) Protein measurement with the Folin phenol reagent. *J Biol Chem* **193**, 265-275.

Masui, Y., Takemoto, T., Sakukibura, S., Hori, H. & Nagai, Y. (1977) Synthetic substrates for vertebrate collagenase. *Biochem Med* **17**, 215-218.

Minor, R. R. (1980) Collagen metabolism. *Am J Pathol* **98**, 225-279.

Nicolaides, K. H., Welch, C. C., MacPherson, M. B. A., Johnson, I. R. & Filshie, G. M. (1983) Lamicel: a new technique for cervical dilatation before first trimester abortion. *Br J Obstet Gynaecol* **90**, 475-479.

Norström, A. (1982) Influence of prostaglandin E_2 on the biosynthesis of connective tissue constituents in the pregnant human cervix. *Prostaglandins* **234**, 361-368.

Norström, A. (1983) Effects of endocervical administration of prostaglandin E_2 on cervical dilatation and connective tissue biosynthesis in the first trimester of pregnancy. *Adv Prostaglandin Thromboxane Leukotriene Res* **12**, 461-464.

Uldbjerg, N., Ekman, G., Malmström, A., Sporrong, B., Ulmsten, U. & Wingerup, L. (1981) Biochemical and morphological changes of human cervix after local application of prostaglandin E_2 in pregnancy (letter). *Lancet* **i**, 267.

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Urinary incontinence during sexual intercourse: a common, but rarely volunteered, symptom

PAUL HILTON

Summary. A total of 400 women referred consecutively to a gynaecological urology clinic was questioned with regard to their sexual activity and were subsequently investigated by cystometry to establish the prevalence of urinary incontinence occurring during intercourse, and to define the urodynamic background of sufferers. Of the 400 women 324 were sexually active, and of these 79 (24%) experienced incontinence during intercourse; in two thirds of sufferers incontinence occurred on penetration, whereas in the remaining one third urine leakage was restricted to orgasm. Of the former group 70% were shown to have genuine stress incontinence and 4% detrusor instability; of the latter, 42% had genuine stress incontinence and 35% detrusor instability. A comparison of cystometric variables in these two index groups and matched controls failed to identify any specific abnormality of bladder function associated with these symptoms.

Sexual dysfunction is frequently present in women with urinary symptoms, the association arising by several mechanisms. First, the urinary symptoms or the reaction of one or other partner to the symptoms may be the direct cause of sexual difficulties, where none previously existed. Second, they may be the apparent cause of a sexual problem, one or other partner either consciously or subconsciously using the urinary symptoms as a means of avoiding sexual contact where there is a pre-existing but unacknowledged sexual problem. Third, urinary complaints may be the presenting symptom of underlying sexual conflict, and may be used as a mechanism for bringing that conflict to the fore (Stanley & Ramage 1984). Sutherst & Brown (1979) found that 43% of incontinent women attending the urodynamic clinic claimed that their urinary problems had adversely affected their sexual relations. There are several reasons for this increase in sexual dysfunction in incontinent patients, such as dyspareunia resulting from urinary dermatitis and from previous incontinence surgery, decreased libido, depression, or simple embarrassment. Urinary incontinence occurring during intercourse is another likely contributory factor, although the complaint is infrequently volunteered, and has not been specifically investigated previously. An attempt has been made to assess the prevalence of this symptom in an incontinent population, and to define the urodynamic background of sufferers.

Patients and methods

The study included 400 women referred consecutively to a gynaecological urology clinic. They were assessed by a standardized questionnaire administered by the physician. They were asked about their sexual activity, and in particu-

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Department of Obstetrics and Gynaecology, University of Newcastle-upon-Tyne, Newcastle-upon-Tyne
PAUL HILTON *Senior Lecturer and Consultant Obstetrician and Gynaecologist*

Correspondence: Mr P. Hilton, Princess Mary Maternity Hospital, Great North Road, Newcastle-upon-Tyne NE2 3BD

lar about any experience of urinary incontinence occurring during intercourse. Those who had noted this symptom were asked whether leakage of urine was associated with arousal, with penetration of the vagina, or specifically with orgasm. Patients were subsequently investigated as indicated by their presenting urinary complaints but all had subtracted dual channel cystometry or videocystourethrography. The relation between the symptoms of incontinence on penetration and on orgasm and the subsequent urodynamic diagnosis was investigated.

A control group was sought for the patients with the symptom of incontinence during intercourse by selecting the next patient referred who matched for age (to within 3 years), and urodynamic diagnosis, who was sexually active, but who did not experience any urinary leakage during intercourse. Cystometric variables were compared between the two symptomatic groups and their respective controls in an effort to identify specific features contributing to the development of this particular symptom, and its timing in relation to sexual activity.

Methods, definitions, and units conform to the standards proposed by the International Continence Society, except where specifically noted (Bates *et al.* 1976, 1977, 1980, 1981).

Results

Of the 400 patients, 324 were sexually active; only two women volunteered the specific complaint of incontinence during intercourse, although on direct questioning a further 77 (24%) had actually experienced the symptom. Of these, 53 women noted incontinence on penetration, and 26 only on orgasm; none related their incontinence purely to arousal or resolution. Thus four initial study groups were identified: 53 who were incontinent on penetration (group 1); 26 who experienced incontinence during orgasm (group 2); 245 who were sexually active but had never experienced urinary incontinence during intercourse (group 3); and 76 women who were not sexually active (group 4). Several women were not having intercourse as a direct result of previous experiences of incontinence during intercourse; these are classified in groups 1 or 2 as appropriate, rather than group 4.

The distribution of urodynamic diagnoses in the four groups is shown in Table 1. Using a χ^2 test on the major diagnostic categories (a, b, c, d, and i) the distributions of diagnoses between those women experiencing incontinence during intercourse (groups 1 and 2) and those without such problems (groups 3 and 4) are significantly different ($P<0{\cdot}02$); similarly the distribution of diagnoses between those with incontinence on penetration (group 1) was significantly different from that seen in women with incontinence on orgasm (group 2) ($P<0{\cdot}02$).

Of the 209 patients shown to have genuine stress incontinence, 48 experienced incontinence during intercourse, 37 (18%) occurring on penetration and 11 (5%) occurring on orgasm. Of the 57 women with detrusor instability, 11 had noted urinary leakage during intercourse in two (3%) of whom it had occurred on penetration and in nine (16%) on orgasm. These symptom distributions were significantly different at

Table 1. Distribution of urodynamic diagnoses in patients with and without the symptoms of urinary incontinence during intercourse

	Urodynamic diagnosis	Incontinence on penetration (group 1) (*n*=53)	Incontinence on orgasm (group 2) (*n*=26)	No incontinence on intercourse (group 3) (*n*=245)	Not sexually active (group 4) (*n*=76)
(a)	Genuine stress incontinence	37 (70%)	11 (42%)	121 (49%)	40 (53%)
(b)	Detrusor instability	2 (4%)	9 (34%)	33 (13%)	13 (17%)
(c)	Genuine stress incontinence plus detrusor instability	5 (9%)	2 (8%)	12 (5%)	3 (4%)
(d)	Voiding dysfunction	4 (7%)	1 (4%)	19 (8%)	4 (5%)
(e)	Impaired bladder compliance	0	0	2 (1%)	1 (1%)
(f)	Hypersensitive bladder	1 (2%)	0	9 (4%)	2 (3%)
(g)	Vesico-vaginal fistula	1 (2%)	0	1	0
(h)	Urethral diverticulum	0	1 (4%)	0	0
(i)	No abnormality detected	3 (6%)	2 (8%)	48 (20%)	13 (17%)

the 5% level using the χ^2 test, and were both significantly different from the distribution seen in the 66 women in whom no urodynamic diagnosis was established. Of the latter only five had experienced leakage on intercourse, three on penetration and two on orgasm.

Controls, matched within the criteria defined earlier, were identified for 70 of the index cases (45 of the 53 in group 1, and 25 of the 26 in group 2). The age, parity, and previous incontinence surgery of the cases and controls are shown in Table 2; there were no significant differences (using the '*t*-test' for continuous and χ^2 test for discontinuous variables). Although the index cases with incontinence on penetration appear to have had rather more pelvic surgery, this was not statistically significant, and reflected the fact that one patient had had eight previous incontinence operations and a hysterectomy. The filling and voiding phases of the cystometrogram were compared for the index cases and controls, and are shown in Table 3. Residual volume, cystometric capacity, pressure rise during filling, pressure rise on provocation, bladder com-

Table 2. Data relating to age, parity, and previous surgical history in index cases and controls for the two symptomatic groups

	Incontinence on penetration		Incontinence on orgasm	
	Index cases (n=45)	Controls (n=45)	Index cases (n=25)	Controls (n=25)
Age (years)				
mean (SD)	42·2 (9·2)	43·2 (8·8)	44·0 (9·8)	43·9 (9·3)
range	21–61	22–64	22–67	25–67
Parity				
median	3	2	3	2
range	0–10	0–7	0–5	1–6
Previous pelvic surgery				
No of women with:				
any pelvic surgery	15	7	7	6
hysterectomy	9	4	3	2
incontinence surgery	10	6	6	6
Total no. incontinence operations	18	9	6	4

Table 3. Cystometric variables in index cases and controls for the two symptomatic groups

	Incontinence on penetration		Incontinence on orgasm	
	Index cases (n=45)	Controls (n=45)	Index cases (n=25)	Controls (n=25)
Residual volume (ml)	20·1 (69·1)	3·6 (7·4)	11·2 (38·0)	6·4 (12·5)
Cystometric capacity (ml)	558·7*(153·0)	493·1*(117·4)	507·0 (167·9)	505·6 (130·9)
Pressure rise—filling ($cm\ H_2O$)	11·7 (10·7)	12·9 (15·1)	15·7 (18·3)	18·9 (20·6)
Pressure rise—provocation ($cm\ H_2O$)	5·1 (13·9)	4·8 (16·3)	3·0 (12·1)	9·1 (22·4)
Bladder compliance ($ml/cm\ H_2O$)	86·6 (109·1)	79·9 (108·4)	61·6 (49·7)	53·5 (37·6)
Maximum voiding pressure ($cm\ H_2O$)	19·0 (20·5)	25·5 (19·0)	16·9 (21·6)	15·3 (18·6)
Peak flow rate (ml/s)	24·5 (10·7)	26·6 (12·1)	25·3 (12·1)	28·1 (12·0)
Urethral resistance ($cm\ H_2O/ml/s^2$)	0·056 (0·08)	0·046 (0·05)	0·142 (0·25)	0·057 (0·04)

Results are mean (SD) values

Significance of difference between index and control group *P<0·05 *t*-test pliance, maximum voiding pressure, peak urine flow rate, and urethral resistance were examined, and compared using the paired *t*-test. Only the cystometric capacity of the group 1 index cases was significantly different from the relevant controls at the 5% level.

Discussion

This study shows that the occurrence of urinary incontinence during sexual intercourse is a much more frequent problem for the incontinent woman than is commonly recognized, being present in one in four of these individuals. The complaint was discovered only on direct questioning in the majority, but all considered it to be a significant problem, and welcomed the opportunity for discussion of what was for many a source of considerable embarrassment and marital disharmony.

The problem may be found in patients with all urodynamic diagnoses, but urinary incontinence occurring on vaginal penetration is more likely with genuine stress incontinence, whereas those women experiencing incontinence on orgasm alone have an increased incidence of detrusor instability. Several of those experiencing incontinence on orgasm during sexual intercourse also had urine leakage occurring during masturbation to orgasm, whereas none of those with incontinence on penetration had had urine leakage with other forms of sexual activity. Despite these associations the only cystometric variable showing any difference between those incontinent individuals who suffer from urinary leakage during intercourse and those who do not appears to be their slightly greater bladder capacity; since both groups had capacities which were well within accepted normal values, it is difficult to attribute any real significance to this finding.

In the male a smooth muscle sphincter is known to exist at the bladder neck level. Its function is probably genital rather than urinary, serving primarily to prevent reflux ejaculation; nevertheless, urinary leakage may also be prevented by this mechanism during extreme sexual arousal and orgasm. However, no such genital sphincter exists in the female, giving her a particular predisposition to this problem.

One might expect that those women with detrusor instability experiencing incontinence on intercourse, especially in association with orgasm, might have higher detrusor pressures than those not so afflicted; this has not been demonstrated, although it is possible that bladder activity during intercourse may be very different from that found in the urodynamic laboratory. Bladder function was not assessed during sexual activity in this study and previous attempts have met with limited success for technical reasons (personal communications by Stanton 1981 and Bhola 1986).

Similarly, those women with genuine stress incontinence who experience loss of urine during penetration of the vagina at intercourse might be expected to have lower urethral resistance than women who do not suffer this symptom, but again this has not been shown in these studies. Urethral pressures were not examined consistently, although a proportion (19 index cases and nine controls) had urethral pressure profiles recorded as part of the investigation of their presenting urinary symptoms; a microtransducer technique was used to examine the urethra at rest and on stress (Hilton & Stanton 1983). The only significant difference identified was a reduction in the pressure transmission ratios in the third quartile of the functional urethral length in the index cases. Whilst it is accepted that the numbers are small, and unmatched with controls, we have previously demonstrated that similarly it is in the third quartile of the functional length that the transmission differences between symptom-free women and those with genuine stress incontinence are maximal (Hilton & Stanton 1983). It is possible therefore that these differences may represent a greater deficiency of pelvic floor function in those women with incontinence during intercourse; however, further investigation of this aspect of the problem is necessary before firm conclusions can be reached.

The treatment of these symptoms remains problematic. The identification of the underlying, or associated, urodynamic abnormality is obviously central to management, although it is my experience that these specific symptoms do not respond to conventional treatments so well as other urinary symptoms. A study of management of these difficult symptoms is in progress. Unfortunately for many women in whom the problem persists after definitive treatment of the urodynamic abnormality, the most appropriate management consists of sympathetic discussion aimed at helping the couple to come to terms with their disability.

References

Bates, C. P., Bradley, W. E., Glen, E. S. *et al.* (1976, 1977, 1980, 1981) First, second, third and fourth reports on the standardisation of terminology of lower urinary tract function. *Br J Urol* **48**, 39-42; **49**, 207-221; **52**, 348-350; **53**, 333-335.

Hilton, P. & Stanton, S. L. (1983) Urethral pressure measurements by microtransducer: results in symptom-free women and in those with genuine stress incontinence. *Br J Obstet Gynaecol* **90**, 919-934.

Stanley, E. M. G & Ramage, M. P. (1984) Sexual problems and urological symptoms. In *Clinical Gynecologic Urology* (Stanton, S. L., ed.), Mosby, St Louis, pp. 398-405.

Sutherst, J & Brown, M. (1979) Sexual dysfunction and urinary incontinence. *Proceedings of the IXth Annual Meeting of the International Continence Society,* Rome.

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A further assessment of the gauze hammock sling operation in the treatment of stress incontinence

J. KERSEY, M. R. MARTIN, P. MISHRA

Summary. A further series of 100 consecutive gauze hammock sling operations for urinary stress incontinence is presented with preliminary urodynamic assessment in all cases and follow-up from 6 months to 5 years. In 63 women the operation was a primary procedure. Modification to the operation included redesign of the shape of the sling, use of increased tension where minor degrees of bladder detrusor instability exist, and use of a suprapubic catheter postoperatively. Of the 100 women 87 were reviewed directly and 12 indirectly; only one was lost to follow-up. After operation, 78% were continent, 17% showed improvement and there were 4% failures. The only serious complication was a pulmonary embolus in one woman but 15 had some voiding difficulty during the follow-up period which responded to urethral dilatation in all but three. There were no fistulas. This improved technique should overcome many of the objections to the sling procedure and is a suitable primary procedure for stress incontinence or for treatment of recurrence after previous alternative procedures.

The gauze hammock sling operation has been criticized because of reported high complication rates including urethral necrosis and bladder neck obstruction, and consequently alternative suprapubic procedures have been widely preferred (Stanton 1978). In a previous series of 105 cases reported by one of us, there were 15 failures and two fistulas (Kersey 1983). We now report a series of a further 100 consecutive cases, with routine urodynamic selection and modification of the sling, resulting in a considerably lower rate of failure and of serious complications.

Patients and methods

Patients were selected from clinical findings in conjunction with urodynamic studies using an Ormed 6 channel analyser and demonstrating stress incontinence in all women. Operation was not performed in women with gross bladder detrusor instability. We define this as a rise in intrinsic bladder pressure or systolic contractions to above 30 cm of water on filling the bladder. A rise between 15 and 30 cm of water pressure was regarded as mild or moderate detrusor instability and operation was carried out.

Postoperative urodynamic studies were considered to be desirable but the department of radiology was unable to accept this additional work load. However, patients with postoperative voiding problems did have this investigation.

Operative technique

The operative technique modified from the work of Aldridge (1942) and Moir (1968)

Basildon Hospital, Basildon, Essex SS16 4NL
J. KERSEY *Consultant Obstetrician and Gynaecologist*
M. R. MARTIN *Consultant Obstetrician and Gynaecologist*
P. MISHRA *Associate Specialist*

Correspondence: J. Kersey

was fully described and illustrated by Kersey (1983).

In this series the design of the mersilene sling has been modified to prevent the previous tendency for the belly of the sling to roll up on elevation of the arms in attaching them to the rectus sheath. This modification can be seen by comparing Figs 1 and 2. The sling is anchored by prolene sutures which, as indicated, ensure distribution of pressure over a wide area. The size of the belly of the sling may be trimmed if required.

At an early stage in the development of the operative technique for the gauze hammock sling, it was decided to assess the degree of resistance when passing a bladder sound into the urethra of a normal nulliparous woman, when doing a simple procedure such as dilation and curettage. When sufficient experience was obtained, this degree of resistance was mimicked by adjusting sling tension in the patients with stress incontinence. Using these criteria, tension has been applied in the operations performed and discussed in this paper.

Where pre-operative urodynamic studies showed mild or moderate degrees of bladder detrusor instability, as defined above, associated with stress incontinence, the operative technique was modified by slight increase in tension of the sling.

In this series we changed to the use of suprapubic catheters after the first 37 patients which resulted in simplified nursing management, and improved patient comfort. The suprapubic catheter was left *in situ* until the residual urine was less than 100 ml. When the Foley catheter was used, a residual urine was performed on the fifth day and the catheter only finally removed when the residual urine was ≤100 ml.

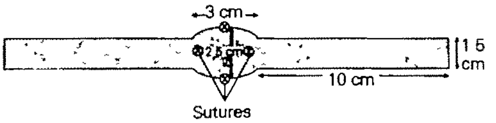

Fig. 1. Previous design of sling.

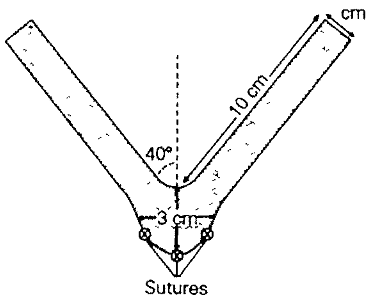

Fig. 2. Present design of sling.

Results

The present series consists of a further 100 consecutive patients treated between 1981 and 1986 with follow-up from 6 months to 5 years. All the patients were invited to attend for special review for the purpose of this study and 87% were directly reviewed in this manner. The remaining 13 who were not available were reviewed indirectly from the case note records of last attendance (n=5), telephone contact (n=4) and letter (n=3). Only one patient was lost to follow-up (Table 1).

Results showed that of 100 patients 78 were no longer incontinent and a further 17 reported improvement to the point where their incontinence was no longer troublesome. There were four failures in whom no improvement occurred, two of these had stable bladders pre-operatively and two had bladder detrusor instability.

The reduction in urinary leakage was confirmed by a marked diminution in the need for sanitary protection (Table 2).

In 22 patients mild or moderate bladder detrusor instability was diagnosed from preoperative urodynamic studies. After surgery 17 of them were continent and five were improved. Four of these five had postoperative urodynamic studies performed and three of them showed persisting bladder detrusor instability.

Complications

Complications are shown in Table 3. There were no deaths in this or the previous series and only one serious complication in a woman who had prolonged postoperative urinary retention and developed a pulmonary embolus which was successfully treated by pulmonary embolectomy. A suprapubic catheter remained *in situ* for 5 months followed by spontaneous return of normal bladder function and no incontinence. During this time cystoscopy and urodynamic investigations failed to disclose any organic cause for her retention of urine.

In this series of 100 patients the mean duration of catheterization was 8·3 days (SD 4·5) with a maximum duration of 26 days catheterization.

In 25 patients, postoperative urinary retention

Table 1. Results of gauze hammock sling operation in 100 patients*

Length of follow-up (months)	No of patients	Previous operations			Continent	Improved	Failed
		0	1	>1			
6–12	25	15	8	2	22	3	—
13–24	23	16	7	—	17	4	2
25–36	18	11	7	—	15	2	1
37–48	13	10	3	—	10	3	—
49–60	19	10	9	—	14	4	1
>60	1	—	1	—	—	1	—
Lost to follow-up	1	1		—			
Totals	100	63	35	2	78	17	4

* By clinical review in 87 patients and indirect review in 13

delayed their discharge from hospital beyond the normal 10 days. Seventeen patients established normal voiding after a delay but in eight urethral dilatation was required before a residual urine of <100 ml could be obtained. The degree of urethral dilatation was to 10 mm. Only one woman required two urethral dilatations.

There were 15 patients who left hospital voiding satisfactorily but subsequently returned complaining of poor urinary stream. Five of them returned within 6 months of operation and nine ≥ 1 year after operation. Urethral dilatation was also performed in this group and satisfactory voiding was obtained in all but three who continue to have slow urinary stream but with no retention.

Discussion

The results of this present series show a substantial improvement over the previous series due almost certainly to the more selective assessment provided by urodynamic studies. The history of sling procedures has been clouded by their reputation for a high prevalence of urinary fistulas (Stanton 1978). It is the authors' contention that the modification of the technique described has virtually eliminated the risk of this complication.

In this series particular attention was given to any complaint of voiding difficulty throughout the follow-up period. This responded to simple urethral dilatation under general anaesthesia in all but three patients. Ideally this group of patients should have been further investigated by uroflowmetry and intravenous pyelography to exclude back pressure on the upper urinary tract. We feel that some voiding difficulties may have been due to our policy of increasing sling tension to overcome minor degrees of bladder detrusor instability for which, in our opinion, alternative treatment is unsatisfactory.

In the present series it has not proved necessary to remove a sling because of a voiding difficulty, although this has been stated to be a complication of sling operations (Stanton *et al.* 1985).

There were four treatment failures of which two had stable bladders, and postoperative urodynamic investigation confirmed persisting bladder neck incompetence presumably due to insufficient tension on the sling. The other two failures were shown to have bladder detrusor instability on both pre- and postoperative urodynamic evaluation.

Table 2. Requirements for sanitary protection in 87 patients clinically reviewed

Sanitary protection	Before operation	After operation
None	8	82
Sometimes	17	2
Always	62	3
Total	87	87

Table 3. Complications of gauze hammock sling operation in 100 patients

Pulmonary embolus	1
Haemorrhage	2
Postoperative urinary retention	25
Late voiding difficulty	15
Wound haematoma/infection	11
Exposure of prolene suture	2

In conclusion we feel that the traditional objections to sling operations have been largely overcome, that the success rate compares favourably with other procedures, and that this is a suitable procedure for the primary treatment of stress incontinence.

Acknowledgments

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References

Aldridge, A. H. (1942) Transplantation of fascia for relief of urinary stress incontinence. *Am J Obstet Gynecol* **44**, 398-411.

Kersey, J. (1983) The gauze hammock sling operation in the treatment of stress incontinence. *Br J Obstet Gynaecol* **90**, 945-949.

Moir, J. C. (1968) The gauze hammock operation (a modified Aldridge-sling procedure). *J Obstet Gynaecol Br Commonw* **75**, 1-9.

Stanton, S. L. (1978) Surgery of urinary incontinence *Clin Obstet Gynecol* **5**, 83-108.

Stanton, S. L., Brindley, G. S. & Holmes, D. M (1985) Silastic sling for urethral sphincter incompetence in women. *Br J Obstet Gynaecol* **92**, 747-750

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Malignant lymphoma presenting as an ovarian tumour: a clinicopathological analysis of 34 cases

H. FOX, F. A. LANGLEY, A. D. T. GOVAN, A. SHIRLEY HILL, M. H. BENNETT

Summary. The clinicopathological features of 34 patients with malignant lymphoma or leukaemia where the initial presentation was as an ovarian tumour are described. Nineteen patients died, usually within 1 year of diagnosis, whilst 15 survived, some for long periods. Factors indicating a poor prognosis were rapid onset of abdominal symptoms, the presence of systemic symptoms, bilateral ovarian tumours, advanced stage and a histological pattern other than that of a B-cell lymphoma. For staging purposes the Ann Arbor method appeared a more sensitive prognostic indicator than did the FIGO staging system. It is suggested that primary malignant lymphomas of the ovary are extremely rare and that for therapeutic purposes all lymphomas of the ovary should be regarded as local manifestations of systemic disease.

In women developing malignant lymphoma or leukaemia the initial presentation of the disease may be as an ovarian tumour. This is far from being a common event and, indeed, of 9500 women suffering from lymphoma in the files of the Armed Forces of Pathology, only 19 (0·2%) presented in this fashion (Chorlton *et al.* 1974). It is thus hardly surprising that, despite the reporting of a few series of such cases (Woodruff *et al.* 1963; Chorlton *et al.* 1974; Paladugu *et al.* 1980; Rotmensch & Woodruff 1982; Osborne & Robboy 1983), the clinicopathological features of lymphoma presenting as an ovarian lesion are still not widely known amongst gynaecologists. We therefore report here the clinical and pathological findings in 34 patients in whom an ovarian tumour was the presenting feature of lymphoma or leukaemia.

Patients and methods

Material from 34 patients was studied. All patients had presented with an ovarian tumour, tissue from which had been submitted to the Ovarian Tumour Panel of the Royal College of Obstetricians and Gynaecologists. Initial study was confined to the examination of haematoxylin and eosin stained sections of formalin fixed, paraffin embedded tissue. Where additional material was available sections were stained with methyl green pyronin and for reticulin. In selected cases immunoperoxidase stains for light chain immunoglobulins, muramidase and alpha-1-antitrypsin were

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Departments of Pathology, University of Manchester and St Mary's Hospital, Manchester
H FOX
F A. LANGLEY

Department of Obstetrics and Gynaecology, Royal Infirmary, Glasgow
A. D. T GOVAN

Department of Pathology, Jessop Hospital for Women, Sheffield
A. SHIRLEY HILL

Department of Pathology, Mount Vernon Hospital, Northwood
M H BENNETT

Correspondence: Professor H Fox, Department of Pathology, University of Manchester, Stopford Building, Oxford Road, Manchester M13 9PT

employed. If a myeloid lesion was suspected sections were also stained for Napthol AS-D chloracetate.

The tumours were classified histologically according to the British National Lymphoma Investigation (BNLI) system of nomenclature (Bennett *et al.* 1974) and staged according to the clinical and operative findings, using both the FIGO system for ovarian tumours and the Ann Arbor method (Carbone *et al.* 1971) for lymphomas (Table 1).

Results

Clinical features

The ages of the patients ranged from 7 to 71 years with a median of 36 years. Twenty of the patients, i.e. nearly two thirds, were aged less than 40 years.

The clinical presentation took one of three forms:

Group 1 (acute onset group). Fourteen patients presented with acute abdominal pain and distension, sometimes accompanied by vomiting. Five women in this group had also noted systemic symptoms such as fever or weight loss.

Group 2 (chronic onset group). Thirteen patients gave a history of gradual onset of abdominal pain (often initially mild) and distension, these symptoms having been present for periods varying from 1 to 6 months. Systemic complaints were not noted in this group.

Group 3 (gynaecological symptoms group). Five women presented with non-specific and probably coincidental gynaecological symptoms, such as menorrhagia or oligomenorrhoea. In two further patients the ovarian mass was an incidental finding, in one woman during pregnancy and in another at surgery for an endometrial adenocarcinoma.

An adnexal mass was palpable in all patients except where the tumour was an incidental intra-operative finding.

Operative findings

The tumours were unilateral in 20 patients and bilateral in 14. In only six instances was the disease confined to the ovaries: local involvement of other tissues was present in 19 (para-aortic nodes in five, the peritoneum in nine and both intra- and extra-peritoneal tissues in four) whilst distant spread, to liver, spleen, kidney, adrenal or pancreas, was noted in 10 patients. Ascites was present in eight patients, blood stained in three.

Using the FIGO staging system, only 10 tumours were put into Stages 1 and 2: 11 were considered to be Stage 3 and 13 were put into Stage 4. According to the Ann Arbor system for staging lymphomas, there were seven in Stage IE, 10 in Stage IIE, none in Stage III and 17 in Stage IV.

Gross appearance of ovarian tumours

The ovarian masses ranged from 5 to 23 cm in their greatest diameter. They were off-white or pinkish-grey and usually reniform with a smooth, bosselated surface. All were solid except for one in which the bilateral tumours contained numerous small blood-filled cysts. Areas of haemorrhage and necrosis were present in only three tumours

Table 1. Ann Arbor staging classification*

Stage	Definition
I	Involvement of a single lymph node region (I) or of a single extra-lymphatic organ or site (IE)
II	Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of an extra-lymphatic organ site and of one or more lymph node regions on the same side of the diaphragm (IIE)
III	Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by localized involvement of the spleen (IIIS), extra-lymphatic site (IIIE) or both (IIISE)
IV	Diffuse or disseminated involvement of one or more extra-lymphatic organs or tissues with or without associated lymph node enlargement

* Adapted from Carbone *et al* (1971).

Histology

All the tumours fell into the general category of non-Hodgkin's lymphoma. Twelve were diagnosed as B-cell lymphomas, six of these being of the follicular centre cell type and six of the diffuse large-cell variety. Five tumours were, on the basis of positive staining for muramidase and alpha-1-antitrypsin, considered to be of histiocytic type. Two tumours were categorized as diffuse undifferentiated large-cell lymphomas and 15 as poorly differentiated lymphocytic/lymphoblastic lymphomas: within this latter group seven tumours were classed as Burkitt's lymphoma, two as T-cell lymphomas and six as lymphoblastic lymphoma (three non-leukaemia related and three leukaemia related).

Treatment

Surgical excision was performed in 30 patients, in six of whom this was the only treatment. Following surgery, five patients received radiotherapy, 10 chemotherapy and nine both radiotherapy and chemotherapy. Chemotherapy was the only form of treatment in two patients whilst a further two were not treated at all.

Outcome and prognostic factors

Nineteen patients died and of these 15 succumbed within 1 year of initial diagnosis, three within 3 years and one after 4 years. Of the 15 patients still alive, five had survived for more than 5 years, three for over 3 years and seven for more than 1 year. Amongst the long-term survivors was one patient who was alive and well 22 years after initial diagnosis and one who was similarly well after 9 years.

Survival in relation to mode of clinical presentation, stage and histological type is shown in Tables 2, 3 and 4. The only other prognostic variable that could be identified was bilaterality, patients with unilateral tumours had a 1-year

Table 2. Survival in relation to clinical presentation

Clinical presentation	Alive	Dead	Median survival (months)
Group 1			
(acute onset)	3	11	4
Group 2			
(chronic onset)	9	4	30
Group 3			
(gynaecological symptoms)	3	4	42

Table 3. Survival in relation to FIGO and Ann Arbor staging

	Alive	Dead	Median survival (months)
FIGO			
Stage 1 and 2	6	4	42
Stage 3	7	4	18
Stage 4	2	11	9
Ann Arbor			
Stage IE	3	4	60+
Stage IIE	8	2	60+
Stage IV	4	13	6+

Table 4. Survival in relation to major histological types

	Alive	Dead
B-cell lymphoma	10	2
Histiocytic lymphoma	0	5
Undifferentiated large-cell lymphoma	0	2
Lymphoblastic lymphoma	5	10

survival rate of 77% whilst of those with bilateral tumours only 46% survived for 1 year.

Discussion

The diagnosis of ovarian lymphoma is almost invariably unsuspected until the tumour is examined histologically, though perhaps suspicions should be aroused in the relatively small proportion of patients with systemic symptoms. Recognition of an ovarian lymphoma requires an index of suspicion by the pathologist for the histological appearances have to be distinguished from those of a chronic inflammatory infiltrate, a granulosa cell tumour, a dysgerminoma, a small-cell carcinoma and metastatic carcinoma: the differential histological diagnosis is fully discussed by Chorlton (1987).

Lymphoma presenting as an ovarian tumour has a poor, but far from hopeless, prognosis. Staging is clearly of prognostic value in these cases and of the two methods employed here the Ann Arbor system emerged as being the more sensitive prognostic indicator, there being a very clear cut difference in mean survival times between patients with Stage IE and IIE tumours and those with Stage IV lesions. The same general pattern was found with FIGO staging but the interval difference between the stages was less pronounced. Our preference for the Ann Arbor system is in conflict with the conclusions of Osborne & Robboy (1983) who, in their analysis of 40 cases, preferred the FIGO method. It is, however, difficult to compare these two series as their histological features differed very widely.

Other factors than stage are also of prognostic significance. A particularly striking finding in this series was that presentation with acute symptoms was associated wtih a particularly poor prognosis: only 28% of women in the acute onset group survived for 1 year compared with 92% in the chronic onset group. Patients who not only had an acute onset of symptoms but had also noted systemic symptoms had an extremely gloomy outlook; all five patients in this series with such symptoms were dead within 3 months of initial diagnosis. Our findings in respect of the prognostic significance of symptomatology accord with those of Paladugu *et al.* (1980) who also stressed that a rapid onset of symptoms was indicative of a very aggressive type of lymphoma.

The histological type of lymphoma was also of some value in assessing the likely outcome. In general terms the prognosis for patients with B-cell lymphomas, whether of the follicular centre cell or the diffuse large-cell type, was good: only two of the 12 patients with this form of lymphoma have so far died and both these survived for over 3 years. By contrast, 17 of the 22 patients with lymphomas other than those of the B-cell type have died.

The treatment of lymphoma lies outside the remit of the gynaecologist but it is worth noting that of the six patients in this series treated by surgery alone two have survived, for 22 years and 3+ years respectively. Of the five patients treated by surgery and subsequent radiotherapy four died whilst of the 10 patients receiving post-operative chemotherapy six are alive. The survival rate for patients treated by both radiotherapy and chemotherapy following surgery was no better than was that utilizing only postoperative chemotherapy. From this superficial analysis it would seem that surgery plus chemotherapy offers the best chance of survival. This series is, however, small and the type of chemotherapy so varied that a truly useful analysis cannot be made.

Although we have generally assumed that the ovarian lymphomas detailed in this study represented an incidental localization of a primarily systemic disease the possibility arises that some were primary lymphomas of the ovary. Doubt has been cast on the existence of such an entity, it being argued that lymphoid tissue is not a normal constituent of the ovary (Nelson *et al.* 1958). Others have, however, maintained that an ovarian lymphoma could arise from hilar lymphoid tissue (Woodruff *et al.* 1963), from lymphocytes in an inflammatory infiltrate (Walther 1934) or from lymphoid tissue in a teratoma (Durfee *et al.* 1937). Fox & Langley (1976) proposed the following criteria for the diagnosis of a primary ovarian lymphoma:

(i) At the time of diagnosis the lymphoma is clinically confined to the ovary and full investigation fails to reveal evidence of lymphoma elsewhere. A lymphoma can still, however, be considered as primary if spread has occurred to immediately adjacent lymph nodes or if there has been direct spread to infiltrate immediately adjacent structures.

(ii) The peripheral blood and bone marrow should not contain any abnormal cells.

(iii) If further lymphomatous lesions occur at sites remote from the ovary then at least several months should have elapsed between the appearance of the ovarian and extra-ovarian lesions.

Application of these criteria to reported cases of ovarian lymphoma indicates that approximately 54 examples of primary lymphoma of the ovary have been recorded (Chorlton 1987) and three of the tumours in this series would also be acceptable as primary ovarian lesions.

However, Paladugu *et al.* (1980) have suggested that the above criteria are insufficiently stringent and proposed that there should be a disease-free interval of at least 60 months following treatment of the ovarian lesion by surgery alone. If this criterion is adopted there have been only five acceptable reported instances of primary ovarian lymphoma (Chorlton 1987) and only one tumour in our series would qualify for this diagnosis. It would be reasonable to conclude therefore that an ovarian lymphoma should always be considered, for therapeutic purposes, as a local manifestation of systemic disease and that to rely upon the possibility of such a lesion being primary to the ovary is unduly optimistic.

References

Bennett, M. H., Farrer-Brown, G , Henry, K. & Jelliffe, A. M. (1974) Classification of non-Hodgkin's lymphomas. *Lancet* **ii**, 405-406

Carbone, P P., Kaplan, H. S., Musshoff, K., Smithers, D. W. & Tubiana, M. (1971) Report of the committee on Hodgkin's disease; staging, classification. *Cancer Res* **3**, 1860-1861

Chorlton, I. (1987) Malignant lymphoma of the female genital tract and ovaries. In *Haines and Taylor's Textbook of Obstetrical and Gynaecological Pathology* (Fox, H., ed.), Churchill Livingstone, Edinburgh, pp. 737-762.

Chorlton, I , Norris, H. J. & King, F. M (1974) Malignant reticulo-endothelial disease involving the ovary as a primary manifestation. *Cancer* **34**, 397-407.

Durfee, H. A., Clark, B. F. & Peers, J. H. (1937) Primary lymphosarcoma of the ovary: report of a case. *Am J Cancer* **30**, 567-573.

Fox, H & Langley, F.A. (1976) *Tumours of the Ovary* Heinemann, London, p. 293.

Nelson, G. A., Dockerty, M. B , Pratt, J. H. & Remine, W. H. (1958) Malignant lymphoma involving the ovaries. *Am J Obstet Gynecol* **76**, 861-871

Osborne, B. M & Robboy, S J. (1983) Lymphoma or leukemia presenting as ovarian tumors: an analysis of 42 cases *Cancer* **52**, 1933-1942.

Paladugu, R. R., Bearman, R. M. & Rappaport, H. (1980) Malignant lymphoma with primary manifestation in the gonad: a clinicopathologic study of 38 patients. *Cancer* **45**, 561-571

Rotmensch, J & Woodruff, J D. (1982) Lymphoma of the ovary· report of 20 new cases and update of previous series *Am J Obstet Gynecol* **143**, 870-875.

Walther, G (1934) Über die Lymphosarkomatose der weiblichen Genitalorgane. *Arch Gynakol* **157**, 44-64.

Woodruff, J. D., Noli Costillo, R. D & Novak, E R. (1963) Lymphoma of the ovary—a study of 35 cases from the Ovarian Tumor Registry of the American Gynecological Society *Am J Obstet Gynecol* **85**, 912-918.

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The incidence and morphology of hydatidiform mole in Abu Dhabi, United Arab Emirates, 1978–1986

IAIN H. GRAHAM, AURORA M. FAJARDO

Summary. In a combined retrospective and prospective study of the frequency and morphology of hydatidiform mole in Abu Dhabi between 1978 and 1986, the incidence at Al Corniche Hospital was 2·02 per 1000 deliveries. Morphological classification showed that complete moles formed 80% of the total.

The frequency of hydatidiform mole varies geographically but little is known of its incidence in the Arabian Peninsula (Bracken *et al.* 1984) or of the relative frequency of the complete and partial forms.

Subjects and methods

We identified the moles evacuated or aborted at Al Corniche Hospital between 1978 and 1984 by inspection of the records in the Pathology Department, and from 1985 to 1986 they were identified at the time of histopathological examination. Two moles were excluded from our series because the patients were referred to Al Corniche Hospital from other hospitals.

The hydatidiform moles were reviewed pathologically to confirm the diagnosis and to classify them as complete or partial. In both types of mole we required a description of gross vesicular change together with microscopically demonstrable trophoblastic hyperplasia and central liquefaction in proportion of the villi. If a fetus or fetal tissue, gestational sac, umbilical cord or part of a normal placenta were present, the mole was classified as partial, otherwise it was considered to be complete. Cytogenetic analysis was not done.

The number of deliveries (livebirths plus stillbirths) in Al Corniche Hospital from 1978 to 1986 (Table 1) was obtained from the hospital records department.

Results

We found 144 hydatidiform moles during the study period, 112 retrospectively and 32 prospectively (Table 2). After review we accepted 126 of these cases as moles and added a partial mole which had been diagnosed as an abortion in 1984. One case was excluded from the series because the histological sections were not available for review and 17 cases were excluded on morphological grounds, in 10 instances because both gross vesicular change and trophoblastic hyperplasia were absent, in five because trophoblastic hyperplasia alone was absent and in two because gross vesicular change alone was absent. These 17 cases were examples of hydropic abortion.

The incidence of all moles during the study period was 2·02, that of complete mole was 1·62 and that of partial mole 0·40, all per 1000 deliveries.

Discussion

Womack & Elston (1985) have written critically of the lack of histological review and of the use of hospital statistics in calculating the incidence of hydatidiform mole. In our study we have attempted to deal with both of these criticisms.

The gross description and histology of all our cases were reviewed using a well-defined set of

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Al Corniche Hospital, Abu Dhabi, United Arab Emirates
IAIN H. GRAHAM *Consultant Pathologist*
AURORA M. FAJARDO *Registrar in Obstetrics*

Correspondence: Iain H. Graham

Table 1. Births in Al Corniche Hospital and Abu Dhabi medical district 1978-1986

	Al Corniche Hospital		Abu Dhabi medical district
Year	Deliveries	Livebirths	Livebirths
1978	4883	4834	6486
1979	5985	5930	7829
1980	7039	6993	9177
1981	8028	7977	10 359
1982	7749	7698	10 782
1983	8019	7950	11 680
1984	7270	7211	11 693
1985	6929	6884	12 036
1986	6943	6906	12 463

Table 2. Hydatidiform mole in Al Corniche Hospital 1978–1986

Year	Original diagnosis of mole	Diagnosis of mole after review	Complete mole	Partial mole
1978	13	8	8	0
1979	24	22	17	5
1980	17	17	10	7
1981	16	13	13	0
1982	19	18	14	4
1983	11	8	6	2
1984	12	11	8	3
1985	15	13	12	1
1986	17	17	14	3

diagnostic criteria, and our diagnosis of hydatidiform mole agreed with that of the reporting pathologist in 88% of the cases.

The Al Corniche Hospital is the largest maternity hospital in the Abu Dhabi medical district. During the period 1978–1986, 98% of all livebirths in the Abu Dhabi medical district took place in hospital (El S. M. Balasy, personal communication) and two thirds of them took place in Al Corniche Hospital (Table 1). Moles from patients referred to Al Corniche Hospital from other hospitals were excluded from our series before pathological review. It is improbable therefore that there was any selection bias in favour of patients with hydatidiform mole.

The incidence of hydatidiform mole in Al Corniche Hospital, Abu Dhabi, between 1978 and 1986 was approximately three times that found in Western Europe and North America (Kolstad & Hognestad 1965; Yen & MacMahon 1968; Ringertz 1970; Bracken *et al.* 1984). The ratio of complete to partial mole, 4 to 1, was identical to that described by Bagshawe *et al.* (1986) for England and Wales and similar to that found by Womack & Elston (1985) in Nottingham.

References

Bagshawe, K. D., Dent, J. & Webb, J (1986) Hydatidiform mole in England and Wales 1973–83. *Lancet* **ii**, 673-677.

Bracken, M. B., Brinton, L. A. & Hayashi, K. (1984) Epidemiology of hydatidiform mole and choriocarcinoma. *Epidemiol Rev* **6**, 52-75.

Kolstad, P. & Hognestad, J. (1965) Trophoblastic tumours in Norway. *Acta Obstet Gynecol Scand* **44**, 80-88.

Ringertz, N. (1970) Hydatidiform mole, invasive mole and choriocarcinoma in Sweden 1958–1965. *Acta Obstet Gynecol Scand* **49**, 195-203.

Womack, C. & Elston, C. W. (1985) Hydatidiform mole in Nottingham: a 12 year retrospective epidemiological and morphological study. *Placenta* **6**, 93-105.

Yen, S. & MacMahon, B. (1968) Epidemiologic features of trophoblastic disease. *Am J Obstet Gynecol* **101**, 126-132.

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Carcinoma of the cervix with massive eosinophilia

D. G. LOWE

Summary. Massive local eosinophilia of 100 or more eosinophils per high power field was found in 3·2% cases of invasive carcinoma of the cervix. The prevalence, length of history before presentation to surgery and histological features were similar in patients from Great Britain and Malawi, but in both populations the mean age at diagnosis was lower than in patients with cervical carcinomas without tissue eosinophilia. In some of the tumours, the malignant cells were very difficult to find because of the eosinophil infiltrate, and misinterpretation as an inflammatory lesion was possible. In the absence of circulating eosinophilia, cervical carcinomas with massive eosinophilia were found to have a better prognosis than tumours without. Five patients had circulating eosinophilia as well as local tumour eosinophil infiltration, and each of them had extensive tumour spread.

Cervical carcinoma is usually associated with a mixed chronic inflammatory cell infiltrate in the stroma around the tumour cells, but in a small number of cases there is a massive stromal infiltrate of eosinophils (Lasersohn *et al.* 1964; Lowe *et al.* 1981*b*).

Cervical carcinoma has a similar range of histological types in different parts of the world (Atkin 1964; Finck & Denk 1970) but varies in the clinical stage at presentation (Ashley 1966). In Malawi, East Africa, cervical cytology screening was not available before 1982, and cervical carcinoma tends to present at a later stage than in Great Britain (Lowe *et al.* 1981*a*). By reviewing cases of cervical carcinoma from these countries, therefore, the effect of the extent of spread of the tumour on the prevalence of massive tissue eosinophilia could be investigated.

Materials and methods

Cases of invasive squamous cell carcinoma of cervix were retrieved from the surgical pathology files of the histopathology departments of St Thomas's Hospital, St Bartholomew's Hospital and Hackney Hospital, London. The histological sections from all such tumours received between 1958 and 1982 at St Thomas's Hospital, and between 1954 and 1984 at St Bartholomew's and Hackney Hospitals, were reviewed. Similar tumours received from Malawi, East Africa, between 1975 and 1978 were also reviewed. There was a total of 1027 cases from the London hospitals and 431 cases from Malawi. From each patient, all of the available sections of tumour and adjacent stroma were examined for eosinophil infiltration. Some aspects of the cases of carcinoma of cervix with massive eosinophilia from Malawi have been described in an earlier paper (Lowe *et al.* 1981*b*).

Histological grading of the carcinomas was based on the terminology of Wentz & Reagan (1959); the descriptive terms large-cell keratinizing, large-cell non-keratinizing and small-cell non-keratinizing carcinoma of the cervix were used.

Sections were screened for eosinophils with a medium power objective lens (final magnification ×125); tumours in which any eosinophils were found by this method were reserved for counting of eosinophils. This was centred on the area of tumour which appeared to have the high-

St Bartholomew's Hospital Medical College, West Smithfield, London EC1A 7BE
D. G LOWE

est number of eosinophils. Tumour eosinophilia was not in all cases a diffuse or uniform phenomenon; in some cases the massive eosinophil infiltrate was present focally, with only moderate eosinophilia in other areas, and random selection of fields for counting was therefore contraindicated. One high power field (HPF) was defined by a ×10 eyepiece lens and a ×40 objective lens, and measured 0·159 mm^2 on the microscopes used. The equivalent of at least 10 HPFs of stroma were counted in all except two cases, and the results were calculated as the number of eosinophils/HPF. In two carcinomas with eosinophilia, the amount of tissue was very small and only five HPFs could be counted. In all of the cases with massive eosinophilia, sections were stained with toluidine blue to demonstrate mast cells.

The ovaries, fallopian tubes, myometrium and lymph nodes were examined for eosinophilia and for metastatic tumour spread. Cervical smears from patients with massive tumour eosinophilia in the cervix in Great Britain were reviewed to see whether eosinophils were present. Smears were not available for the Malawi cases.

The ages of the patients, the length of history before presentation, and the length of survival after diagnosis were obtained from the case notes in the British series. Clinical information on the Malawi cases was derived from the request forms which accompanied the histological specimens; in most cases the patient's age was an approximation, and this was therefore rounded to the nearest decade. In all of the hospitals in the study the staging system of the International Federation of Obstetrics and Gynecology (FIGO) was used (FIGO 1978). No follow-up information was available on the Malawi cases.

To investigate whether massive tumour eosinophilia could be regarded as a discrete entity or simply the upper end of a uniformly increasing intensity of eosinophil infiltration, the number of eosinophils was counted in a series of 430 randomly selected cases of cervical carcinoma irrespective of whether eosinophils were found on low power scanning.

Blood eosinophil counts

Almost all of the patients from Great Britain in whom tumour eosinophilia was found had had a routine full blood count and differential count on admission to hospital, and the blood eosinophil count was therefore recorded Blood eosinophil counts were not available on the African cases.

Cases excluded from the study

Eosinophils would be expected around areas of necrosis in cervical carcinomas (Goswami 1966; Tavassoli 1981), in schistosomal infection of the cervix (Tiltman 1978), and in previously biopsied cases (Tiltman 1978) When necrosis of over two HPFs or schistosomal infection were found, the cases were rejected from the study. Where tissue eosinophilia was not found in the initial biopsy, the case was also rejected.

Results

The mean age of the women with eosinophilic carcinomas in the British series was 43 years (range 26–67 years) and in the Malawi series 38 years (range 30–60 years). There was no significant difference between the mean ages in the two populations, nor between the lengths of history before diagnosis or clinical stage of the tumours

Regression analysis of the distribution of eosinophil counts showed that the tumours with an eosinophil infiltrate of ≥100 eosinophils/HPF constituted a distinct group and were not simply one end of a continuously increasing, uniform range of counts. (This does not, of course, mean that there is great importance in the choice of 100 eosinophils/HPF; if the figure of 90 or 80 eosinophils/HPF were taken as the cut-off point there would be a similar group delineated, though the distinction would be less clear.)

No aetiological explanation for tumour eosinophilia was found in the history, clinical examination or histological specimens other than the presence of the tumour itself. Invasive cervical carcinoma is considerably commoner in East Africa than in Europe or North America (Edington & Gilles 1976) but the prevalence of massive eosinophilia in cervical carcinoma was similar in the Malawi and British cases. There was no relation between hormonal contraception and massive tumour eosinophilia in the cervical tumours from Britain or Malawi. The finding of massive eosinophilia before 1960 and in Malawi made an allergic reaction to vaginal deodorants as a cause for cervical eosinophilia unlikely.

Table 1. Summary of British and Malawian cases of squamous cell carcinoma of cervix with massive tissue eosinophilia

	No. of cases	No. with massive eosinophilia	Cell type of eosinophilic tumours
British cases	1027	34 (3·3%)	31 LCNK 2 LCNK/LCK 1 LCNK/SCNK
Malawi cases	431	13 (3·0%)	12 LCNK 1 LCK

LCNK, Large-cell non-keratinizing carcinoma; LCK, large-cell keratinizing carcinoma; LCN/LCNK, mixed large-cell keratinizing and non-keratinizing carcinoma; LCNK/SCNK, mixed large- and small-cell non-keratinizing carcinoma.

Cervical carcinoma with eosinophilia in Great Britain

The numbers and histological grades of the cervical carcinomas with massive eosinophilia are given in Table 1. All of the 34 tumours with massive eosinophilia were large-cell non-keratinizing ('moderately differentiated') squamous cell carcinomas of cervix. Two also had smaller areas of large-cell keratinizing carcinoma, and one had areas of small-cell non-keratinizing carcinoma.

The histological appearances of the cervical carcinomas with massive tissue eosinophilia were similar to those described in other carcinomas with eosinophilia (Bostrom & Hart 1981; Lowe *et al.* 1984) (Fig. 1). Some features, however, were found that had not been reported before. In some tumours the islands of neoplastic cells contained few eosinophils in their

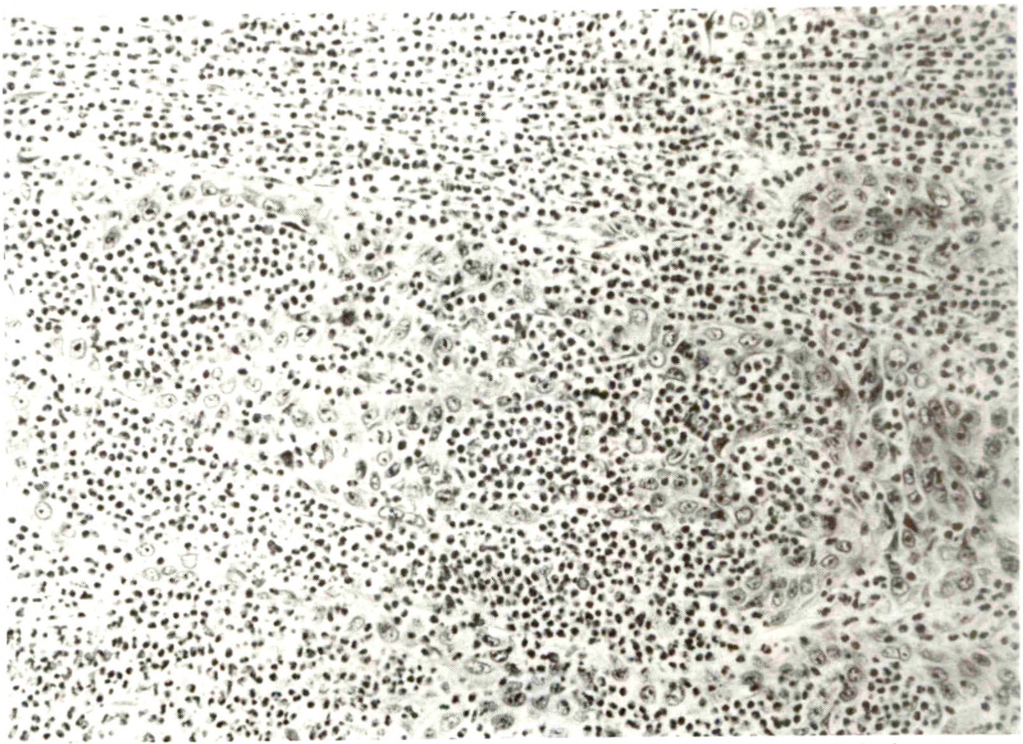

Fig. 1. Cervical carcinoma with massive eosinophilia. Almost all of the inflammatory cells in the stroma were eosinophils. Haematoxylin and eosin ×100.

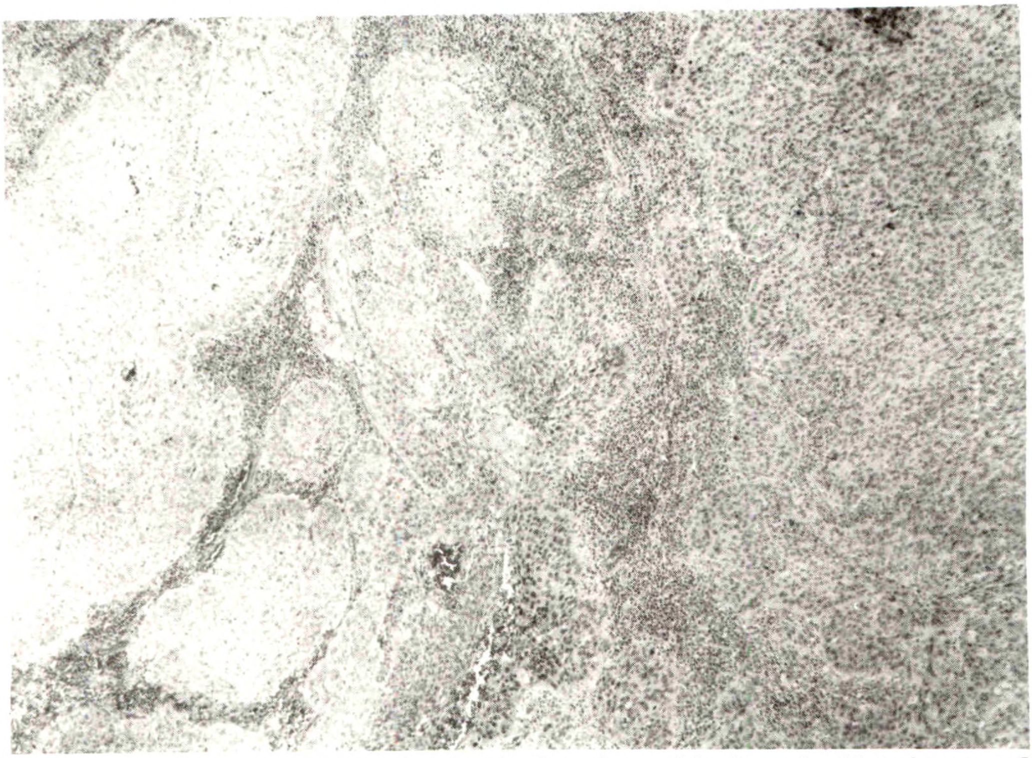

Fig. 2. The area of cervical carcinoma on the left of the photomicrograph has few eosinophils in the stroma. On the right, where there is massive eosinophilia, the contour of the tumour islands is irregular and ill-defined. Haematoxylin and eosin ×40.

centres but had eosinophils in a row around the advancing edge of the tumour. At the other end of the spectrum, cervical carcinomas with a particularly dense infiltrate had eosinophil microabscesses within tumour cell islands. The clinical data in these cases suggested that microabscesses occurred in relatively long-standing lesions, and there might therefore be a spectrum of eosinophilia in tumours from linear infiltration through diffuse intercellular infiltration to microabscess formation. The stimulus to interepithelial migration appeared to be diffuse, and not dependent on focal stimuli such as degenerating cells.

In 19 of the tumours studied, massive eosinophilia was focal. The tumour cells in areas with and without eosinophilia had similar characteristics; the histological arrangement of the tumour cells, on the other hand, was different. In non-eosinophilic areas the outlines of the tumour islands were clearly demarcated, while in eosinophilic areas the trabeculae and islands of tumour cells were more ragged and the borders were difficult to define (Fig. 2). There was no evidence of frank necrosis in the eosinophilic areas but pyknotic tumour cell nuclei appeared to be more numerous than in non-eosinophilic areas.

Most of the lymph nodes which were available for examination were tumour-free and non-eosinophilic, but in two specimens metastatic carcinoma was found. The tumour cells in these were very similar to those of the primary tumour, and were difficult to find amongst the massive infiltrate of eosinophils. In two others the lymph nodes had massive sinus eosinophilia without demonstrable metastatic tumour.

Five patients in the British series who had massive tumour eosinophilia also had circulating eosinophilia (Table 2). These patients all had Stage III or IV disease, and survived for an average of 16 months. The other patients in the British series did not have circulating eosinophilia (Tables 2 & 3). Two patients died, 2 years and 7 years after initial diagnosis, from recurrent disease. The others are all alive and clinically free from tumour. Their survival times vary from 6 months to 28 years (mean 10 years). The six patients with Stage III disease who did not have circulating eosinophilia are still alive,

Table 2. British patients with carcinoma of cervix with massive eosinophilia who had died, ranked by length of survival

Patient	Age (years)	Length of history (months)	Stage	Blood eosinophilia	Interval between diagnosis and death (years)
1	44	5	III	Yes	0·75
2	38	3	III	Yes	1
3	51	4	III	Yes	1
4	47	2	IV	Yes	1
5	39	—	Case notes missing		1
6	33	—	Case notes missing		1
7	59	5	III	No	2
8	53	0	III	Yes	3
9	41	—	II	No	7

Table 3. British patients with carcinoma of cervix with massive eosinophilia who were still alive, ranked by time after diagnosis

Patient	Age (years)	Length of history (months)	Stage	Blood eosinophilia	Survival since diagnosis (years)
10	48	3	II	No	0·5
11	39	3	I	No	1
12	54	2	I	No	1
13	35	1	I	No	1
14	39	2	I	No	2
15	59	3	I	No	3
16	62	—	I	No	4
17	43	5	I	No	5
18	37	1	III	No	6
19	26	0	I	No	8
20	30	1	I	No	9
21	33	—	III	No	10
22	37	2	—	No	10
23	32	0	II	No	10
24	29	—	III	No	11
25	67	—	II	No	11
26	30	5	I	No	12
27	31	24	III	No	13
28	41	—	II	No	14
29	47	3	II	No	16
30	46	2	II	No	16
31	45	—	III	No	17
32	42	2	III	No	20
33	47	—	—	No	28
34	46	2	II	No	Lost to follow-up

and have survived so far between 6 and 20 years (mean 13 years).

Assessment of the prognostic importance of tumour eosinophilia in this study was difficult because the cases were derived from patients presenting between 1954 and 1984; the treatment of the cases diagnosed in the 1960s might therefore have been different from that used 20 years later. However, the survival figures for carcinoma of the cervix collected by FIGO have changed little for each clinical stage over the period studied (FIGO 1985), and so provide some indication of the expected prognosis which could be compared with that found in the cases with tumour eosinophilia. The 5-year survival figures for the British series are given in Table 4.

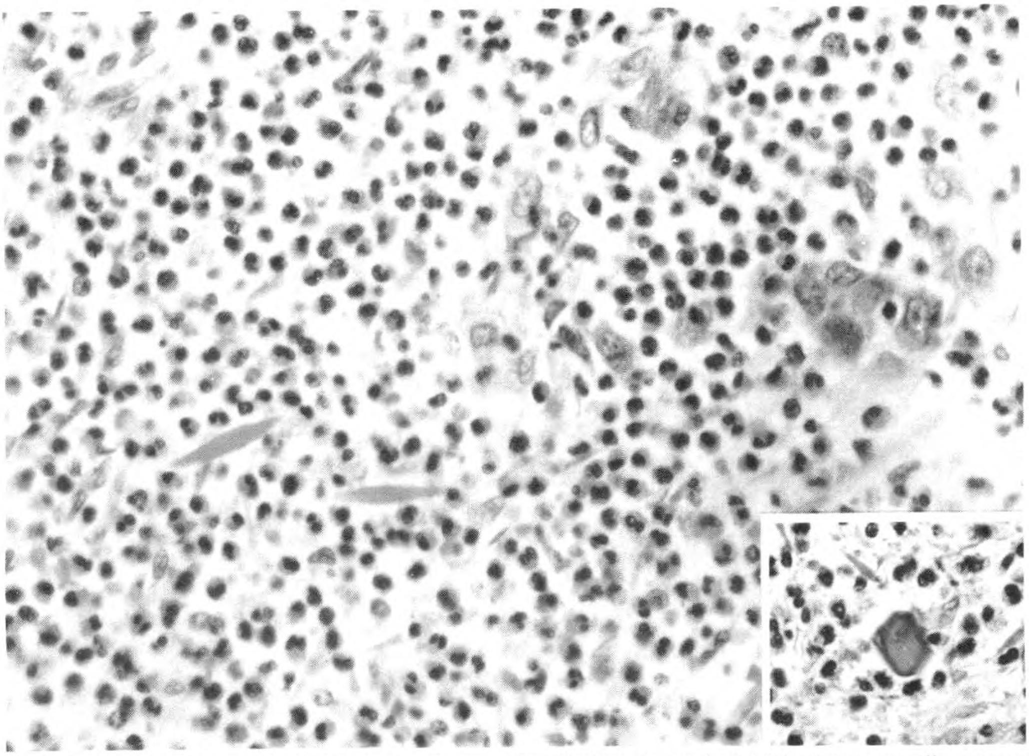

Fig. 3. Charcot-Leyden crystals in the stroma of a case of cervical carcinoma from Malawi; tumour cells were very sparse and difficult to find in some areas. Haematoxylin and eosin ×650.

The expected survival figures are taken from the FIGO returns for 1976–78 (FIGO 1978).

Cervical carcinoma with eosinophilia in Malawi

The histological features of the tumour cells and eosinophil infiltrate were almost identical with those of the British series. Charcot-Leyden crystals were present in tissue sections in four cases. There were dense collections of these acidophilic, bipyramidal, elongated crystals lying in the stroma between tumour cells; transected crystals had the typical hexagonal appearance (Fig. 3). The tumour cells in the areas of the crystals were similar to those elsewhere, and there was no apparent relation between the presence of crystals and the clinical details. There did, however, appear to be a relation between Charcot-Leyden crystals and the density of the eosinophilia, which was very high in the area of the crystals. A further factor applicable in each of the cases was that the crystals were found deep within the cervical stroma. There might, therefore, have been preservation of the crystals from solution in formol saline during fixation, though this seems unlikely as they are very poorly soluble (Tavassoli 1981). Only occasional mast cells were present, and these were greatly outnumbered both by eosinophils and Charcot-Leyden crystals.

The clinical details of the Malawi cases are listed in Table 5; follow-up data were not available on these cases.

Cervical cytology

All of the patients in the British series who had cervical carcinomas with massive eosinophilia had had previous cervical cytology. There were small numbers of eosinophils on 18 of the smears, but in none was there a degree of eosinophilia equal to that seen histologically.

Discussion

The cervical tumours with massive eosinophilia from both Malawi and Great Britain had many histological features in common, though large numbers of Charcot-Leyden crystals were found only in those from Malawi. There was no evidence that the crystals might have been derived from mast cells, as has been described by Archer

Table 4. Prognosis of cervical carcinoma with tumour eosinophilia—5-year survival figures

		5-year survival Actual	
FIGO stage	Expected, all cases	All eosinophilic carcinomas	Eosinophilic carcinomas without blood eosinophilia
I	78·1%	4/4 (100%)*	4/4 (100%)*
II	57·0%	6/6 (100%)†	6/6 (100%)†
III	31·0%	6/11 (55%)	6/7 (86%)
IV	7·8%	0/1	—

* A further six patients were still alive, but had not yet survived for 5 years.
† One other patient was alive but only so far for 6 months after diagnosis.

Table 5. Malawi patients with carcinoma of cervix with massive eosinophilia, ranked by clinical stage

Patient	Age* (years)	Length of history (months)	Clinical stage
1	—	3	I
2	30	—	I
3	40	—	I
4	60	2	I
5	30	—	II
6	30	—	II
7	40	3	II
8	50	7	II
9	50	2	II
10	30	—	III
11	30	1	III
12	40	1	III
13	60	—	—

* To the nearest decade.

& Blackwood (1965), and their distribution suggested that particularly high numbers of eosinophils were necessary for crystal formation. Adjacent tumour cells showed no appreciable morphological changes which might have indicated that tumour cell degeneration or death was occurring as a consequence of the crystal lysophospholipase. There was no thrombus formation in small vessels adjacent to the tumours, and there was no histological evidence of a primary vasculitis or granuloma formation which might have suggested that the eosinophilia was a reaction to local antigen/antibody complex deposition.

In the tumours in which massive eosinophilia was focal, the histological appearances suggested that the architectural differences were almost certainly the consequence of the presence of the eosinophils and not the cause of it. If the tissue eosinophilia were due to a chemotactic factor produced by the tumour cells themselves, as has been proposed in cervical and bronchial carcinomas (Wasserman *et al.* 1974; Goetzl *et al.* 1978; Inoue *et al.* 1981), then secretion in some cases must be from only a proportion of the tumour cells, and these have no distinct cytological features.

Eosinophils were present in the highest numbers deep within the tumours, and there were relatively few at the tumour surface. This corresponded with the absence or paucity of eosinophils on the available cytological examination and supported the cytological finding that diagnosis of eosinophilic tumours by examination of cytological preparations for eosinophils would not be efficient.

Metastatic deposits in lymph nodes had the same features as the parent tumour; the neoplastic cells were broken up into small groups by a dense eosinophil infiltrate, with features similar to those described by Inoue *et al.* (1981). A possible cause for the eosinophilia in nodes without metastases might have been a soluble factor elaborated at the primary tumour site which was either chemotactic for eosinophils, or fixed them in the tissues, or both. A soluble chemotactic factor has been isolated from homogenized tumour tissue (Wasserman *et al.* 1974; Inoue *et al.* 1981) and this could, therefore, have accounted for the eosinophilia in the draining lymph nodes. It is interesting that not all of the nodes in patients with eosinophilic carcinomas were affected by sinus eosinophilia; there was no apparent histological reason why a soluble factor should be localized to the tumour in some cases and not others. This discrepancy could perhaps be because there was secretion of eosinophilochemotactic factors by T-lymphocytes from the tumour (Hirashima *et al.* 1986), which in some cases might have migrated from the primary tumour site and become fixed in regional lymph nodes.

On some of the tiny fragments of tissue from the biopsy specimens in the series, only eosinophils and cervical stromal cells were present. In other fragments, single tumour cells were widely separated from each other by the massive eosinophil infiltrate and were difficult to find. There was therefore the possibility of misdiagnosis of the rare condition of eosinophilic cervicitis (d'Ablaing & Beck 1977). Similar difficulty in finding carcinoma cells was encountered when examining lymph nodes for metastatic carcinoma. It is important, therefore, that carcinoma is considered as a possible cause for tissue eosinophilia before a diagnosis of an inflammatory cause is accepted. Immunocytochemical staining of epithelial cells with epithelial membrane antigen and other markers can be useful in these cases (unpublished observations).

The mean ages of the women with cervical carcinomas with massive eosinophilia in the British and African series (43 and 38 years respectively) were lower than for those with non-eosinophilic tumours from the same populations. The mean age at presentation of all patients with cervical cancer in Great Britain is 54 years (range 15–85 years) (OPCS 1980) and in Malawi is in the decade 40–50 years (Lowe *et al.* 1981*a*).

In the patients from Great Britain with cervical carcinoma with tumour eosinophilia who did not have circulating eosinophilia, the range of clinical stages was similar to that in the Malawi series. Two patients died from recurrent carcinoma but all the others are still alive and disease free. The number of patients was relatively small and the follow-up times on some have not reached 5 years, but patients who had tumours which had an eosinophil infiltrate and who did not have circulating eosinophilia appeared to have a better prognosis than would be expected from general, unselected series comprising mainly non-eosinophilic cervical carcinoma. Other workers have also reported a relatively favourable prognosis in carcinoma of cervix with tissue eosinophilia (Bailar *et al.* 1966; Pastrnák & Jansa 1984).

The prognosis of cervical carcinoma in general has been found to be worse for women below 46 years of age than for older women (Sidhu *et al.* 1970) though this has been questioned recently (Smales *et al.* 1987). In the British series of cervical tumours with massive eosinophilia, 29 patients (85%) were less than 46 years old. Three of them had died, two of whom had circulating eosinophilia. The other 26 were still alive, from 1 to 17 years after diagnosis. The survival figures suggested, therefore, that cervical tumours with tissue eosinophilia in younger women were not as aggressive as non-eosinophilic cervical carcinomas. Circulating eosinophilia in cervical carcinoma, on the other hand, appears to be associated with a poor prognosis, as has been found in other series (Isaacson & Rapoport 1946; Bostrom & Hart 1981; Slungaard *et al.* 1983; Lowe *et al.* 1984).

References

Archer, G. T. & Blackwood, A. (1965) Formation of Charcot-Leyden crystals in human eosinophils and basophils and study of the composition of isolated crystals. *J Exp Med* **122,** 173-180.

Ashley, D. J. B. (1966) Evidence for the existence of two forms of cervical carcinoma. *J Obstet Gynaecol Br Commonw* **73,** 382-389.

Atkin, N. B. (1964) Nuclear size in carcinoma of the cervix: its relation to DNA content and to prognosis. *Cancer* **17,** 1391-1399.

Bailar, J. C., Thomas, L. B., Thomson, A. D., Eisenberg, H. & Vick, R. M. (1966) Morphology and survival rates of cervical cancer in Connecticut and Southwest England. *Natl Cancer Inst Monogr* **19,** 385-403.

Bostrom, S. G. & Hart, W. R. (1981) Carcinomas of the cervix with intense stromal eosinophilia. *Cancer* **47,** 2887-2893.

D'Ablaing, G. & Beck, M. (1977) Congenital neonatal eosinophilic cervicitis. *Am J Obstet Gynecol* **129,** 345-346.

Edington, G. M. & Gilles, H. M. (1976) *Pathology in the Tropics*. Edward Arnold, London.

FIGO (1985) *Annual Report on the Results of Treatment in Gynecological Cancer*. Volume 19, Results obtained in 1976 to 1978, inclusive. FIGO, Stockholm.

Finck, F. M. & Denk, M. (1970) Cervical carcinoma. Relationship between histology and survival following radiation therapy. *Obstet Gynecol* **35,** 339-343.

Goetzl, E. J., Tashjian, A. H., Rubin, R. H. & Austen, K. F. (1978) Production of a low molecular weight eosinophil polymorphonuclear leukocyte chemotactic factor by anaplastic squamous cell carcinomas of human lung. *J Clin Invest* **61,** 770-780.

Goswami, P. K. (1966) Effects of local eosinophilia on isologous tumour growth in mice. *Indian J Med Sci* **20,** 123-125.

Hirashima, M., Sakata, K., Tashiro, K., Ohmori, J., Iyama, K., Tsuda, H., Nagai, T., Hiraoka, T. & Kimura, T. (1986) Spontaneous production of eosinophil chemotactic factors by T lymphocytes from patients with subcutaneous angioblastic lymphoid hyperplasia with eosinophilia. *Clin Immunol Immunopathol* **39,** 231-241.

Inoue, T., Iwasaki, K., Chihara, T. & Torisu, M. (1981) Cervical carcinoma and eosinophil. I. Eosinophil chemotactic factor derived from invasive cervical carcinoma with eosinophil infiltration. *Clin Immunol Immunopathol* **21,** 320-331.

Isaacson, N. H. & Rapoport, P. (1946) Eosinophilia in malignant tumours: its significance. *Ann Intern Med* **25,** 893-902.

Lasersohn, J. T., Thomas, L. B., Smith, R. R., Ketcham, A. S. & Dillon, J. S. (1964) Carcinoma of the uterine cervix. *Cancer* **17,** 338-351.

Lowe, D., Jorizzo, J., Hutt, M. S. R. & Chiphangwi, J. (1981*a*) Cervical carcinoma in Malawi: a histopathological study of 460 cases. *Cancer* **47,** 2493-2495.

Lowe, D., Jorizzo, J. & Hutt, M. S. R. (1981*b*) Tumour-associated eosinophilia: a review. *J Clin Pathol* **34,** 1343-1348.

Lowe, D., Fletcher, C. D. M. & Gower, R. L. (1984) Tumour-associated eosinophilia in the bladder. *J Clin Pathol* **37,** 500-502.

OPCS (1980) *Cancer Statistics* Series MB1 12. Her Majesty's Stationery Office, London.

Pastrnák, A. & Jansa, P. (1984) Local eosinophilia in stroma of tumors related to prognosis. *Neoplasma* **31,** 323-326.

Sidhu, G. S., Koss, L. G. & Barber, H. R. K. (1970) Relation of histologic factors to the response of stage I epidermoid carcinomas of the cervix to surgical treatment: analysis of 115 patients. *Obstet Gynecol* **35,** 329-338.

Slungaard, A., Ascensao, J., Zanjani, E. & Jacob, H. S. (1983) Pulmonary carcinoma with eosinophilia. *N Engl J Med* **309,** 778-781.

Smales, E., Perry, C. M., Ashby, M. A. & Baker, J. W. (1987) The influence of age on prognosis in carcinoma of the cervix. *Br J Obstet Gynaecol* **94,** 784-787.

Tavassoli, M. (1981) Eosinophil, eosinophilia and eosinophilic disorders. *CRC Crit Rev Clin Lab Sci* **5,** 329-338.

Tiltman, A. J. (1978) Eosinophilic infiltrates in carcinoma of the urinary bladder unassociated with schistosomiasis. *J Pathol* **126,** 79-83.

Wasserman, S. I., Goetzl, E. J., Ellman, L. & Austen, K. F. (1974) Tumour-associated eosinophilotactic factor. *N Engl J Med* **290,** 420-424.

Wentz, W. B. & Reagan, J. W. (1959) Survival in cervical cancer cases with respect to cell type. *Cancer* **12,** 384-388.

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Use of tissue expansion techniques to create skin flaps for vaginoplasty. Case report

RICHARD J. LILFORD, DAVID T. SHARPE, DAVID F. M. THOMAS

Case report

A 14-year-old schoolgirl with primary amenorrhoea had had abdominal pain for 5 months. Puberty had started at the age of 11 and was now complete. Cryptomenorrhoea had been diagnosed at her local hospital and had been drained vaginally 2 weeks preceding referral. The vagina was totally absent throughout most of its length and 2·5 inches of blunt dissection had been necessary to reach the menstrual fluid The referring gynaecologist could palpate the cervix in the short upper vagina. The drainage track had closed following this procedure and a further attempt to establish a permanent connection between the upper reproductive tract and the exterior had also failed. The patient was referred with recurrence of acute abdominal pain and a high temperature.

On admission to our hospital the fistulous tract between a normal vaginal introitus and the uterus had completely stenosed. Ultrasound demonstrated a normal renal system and a pelvic mass. Laparoscopy confirmed the diagnosis of pyometra and demonstrated a large unilateral tubo-ovarian abscess Numerous endometriotic deposits were also noted in the pelvis. The abscess was drained through the laparoscope by means of a Verres' needle.

The patient was then given intravenous metronidazole, gentamicin and a depot injection of a long-acting gonadotrophin-releasing hormone (GnRH) agonist (Zoladex). The antibiotics were used to treat the pelvic infection and the synthetic GnRH agonist to prevent any further menstrual blood accumulation prior to definitive surgery (Meldrum *et al* 1982). The pus aspirated in the operating theatre confirmed sensitivity to the above antibiotics. The options for definitive vaginal construction were discussed frankly with the patient and her parents. The technique of amnion vaginoplasty, hitherto the first author's operation of choice for partial and complete Mullerian agenesis (Ashworth *et al.* 1986), was considered less suitable in this case; the operation site would be heavily infected and the accumulation of purulent material could lead to a dangerous pelvic cellulitis. In addition, the patient was unlikely to be sexually active for at least a year or so and contraction of the new vaginal wall would be probable. A bowel graft was considered seriously but it was felt that the possibility of full thickness flaps of expanded labial skin would have many advantages. The patient and her parents agreed to the new procedure, although it was pointed out that this was experimental and might fail. The more radical operation of bowel pedicle vaginoplasty was therefore held in reserve.

Tissue expanders were inserted under general anaesthesia; incisions were made over each groin and blunt dissection was used to create tracks to the internal aspects of the labia minora (Fig. 1). Tissue expanders were then buried under the labial skin. Each expander was connected by flexible plastic tubing to a valve and reservoir in the groin The skin was closed over the original incision. Each of the expanders was then inflated to 40 ml. This caused the labia to expand considerably but there was no decreased skin perfusion at this volume (Fig. 2). Ice packs were applied to the vulva for the first 12 h postoperatively to limit the oedema of surgery. Over

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St James's University Hospital, Leeds LS9 7TF
Department of Obstetrics and Gynaecology
R J. LILFORD

Department of Paediatric Surgery
D F M. THOMAS

Department of Plastic Surgery, Bradford Royal Infirmary, Duckworth Lane, Bradford
D. T. SHARPE

Correspondence: R J. Lilford

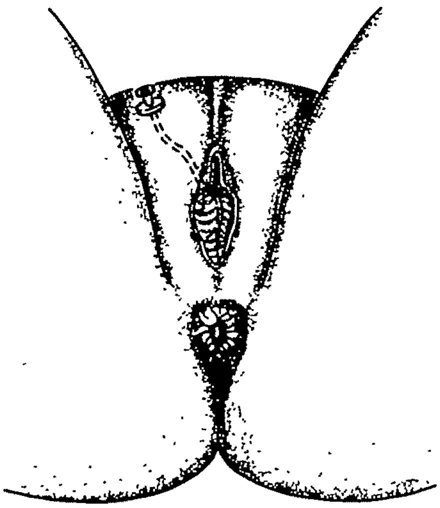

Fig. 1. Diagram showing position of expanders, flexible tubing and valve. The valve was buried in the inguinal area at a distance from the labial expanders. Inflation of the expanders themselves is achieved by passing a small (25 gauge) needle into the valve and injecting normal saline into the system. In future we plan to bring the valve out through the skin and thereby make it easier for the patient to inflate her own expanders as an outpatient.

the next 18 days the expanders were further inflated by 12–15 ml every 3 days. Testosterone cream was applied to the external portion of the labial skin. Chafing of the opposing medial aspects of the labial swellings was prevented with lubricating jelly. The skin of the labial area became reddened due to the hyperaemia which is known to accompany skin expansion in all areas. There were no complications of infection, pain or haematoma. The valves and reservoirs of the tissue expanders were, however, buried under the skin to reduce the chance of infection and a 25 gauge needle was used for inflation. Analgesia was required each time. Throughout this period the patient remained in the ward but tuition was arranged through the hospital teacher. The patient was encouraged as much as possible and developed very good rapport with both medical and nursing staff. Antibiotic treatment was continued throughout this period to prevent a flare-up of the pelvic inflammatory disease. A further dose of the long-acting GnRH agonist was administered after 2 weeks.

Definitive surgery was carried out 18 days later; the tissue expanders had been inflated to 120 ml on each side. Sinoscopy was performed with a paediatric cystoscope which was used to re-establish the fistulous tract between the normal vestibule and upper genital tract, releasing foul-smelling pink fluid. Each tissue dilator was then blown up to 200 ml intermittently for 3 min at a time and this was repeated three times (Fig. 3), after which the tissue expanders were removed. We had created two large folds of labial skin that were at least 3 inches long and had non-hair-bearing skin on their medial aspects.

The abdominal cavity was opened through a Pfannenstiel incision. Residual pus in the right ovary was drained and it was noted that fimbrial damage had occurred on this side. The other tube, although slightly reddened, did not look severely damaged and the fimbria were intact. A blunt probe was inserted into the uterine cavity, through the fundus of the uterus and passed down through the cervix. This manoeuvre was carried out in order to guide the subsequent dissection from below. Lateral incisions (at 3 and 9 o'clock) were made in the vestibule between the now expanded labia minora. Digital dissection was carried out through this opening in the area of the re-established fistulous tract lying between the bladder and rectum. The fistulous tract was excised. A large vaginal pouch was thereby created in the correct anatomical position for the vagina and dissection was carried up to meet the cervix. There was very little upper vaginal skin but, fortunately, the cervix was present. This was dilated to Hegar 7 and further infected material then drained from the uterus. Two large full-thickness flaps, based posteriorally, were raised from the inner aspects of each labial swelling (Fig. 4). These were turned into the vagina to line each side of the newly created cavity (Fig. 5). The upper edges of these flaps were sutured to the vaginal edge adjacent to the cervix. The posterior margins of the flaps were not sutured, but were allowed to lie against each other posteriorally in order to leave some slack in the newly created vaginal tube and to allow any fluid accumulation under the flaps to drain. The bare areas created by removal of the skin flaps were closed over corrugated drains which were led out through the original inguinal incisions. The vaginal introitus looked relatively normal after this procedure (Fig. 6) and two fingers could be inserted into the new vagina. A large Readi-Vac drain was placed in the pouch of Douglas and led out through the abdominal

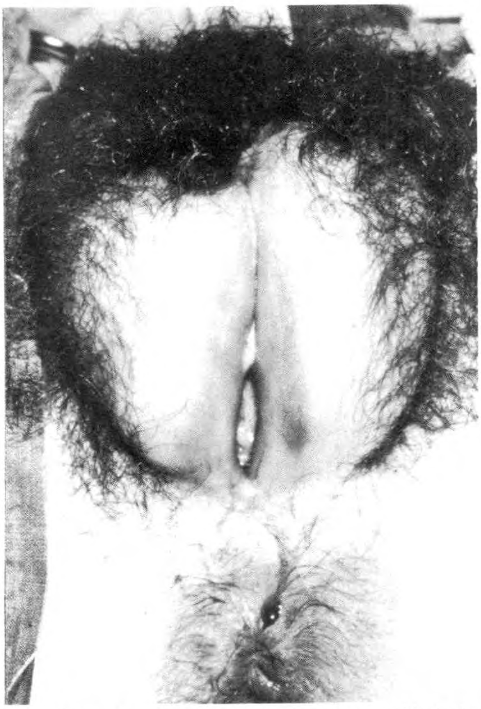

Fig. 2. The vulva after the initial insertion and inflation of the tissue expanders.

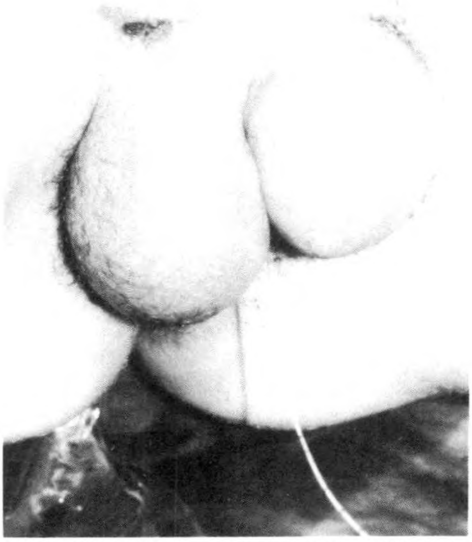

Fig. 3. Final volume (200 ml) of the labial tissue expanders.

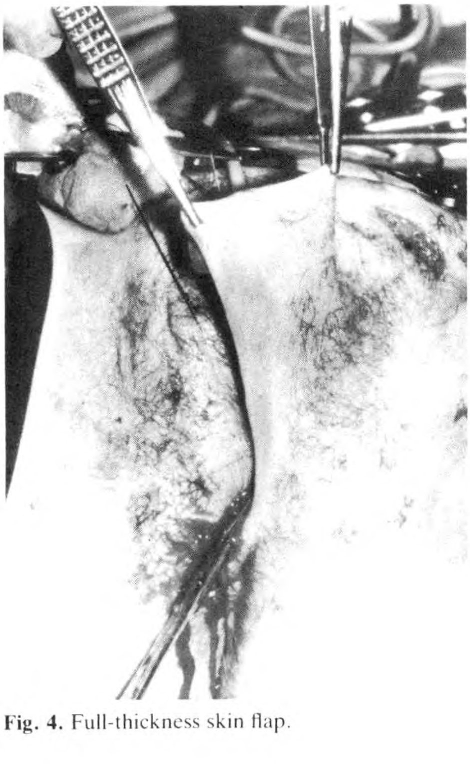

Fig. 4. Full-thickness skin flap.

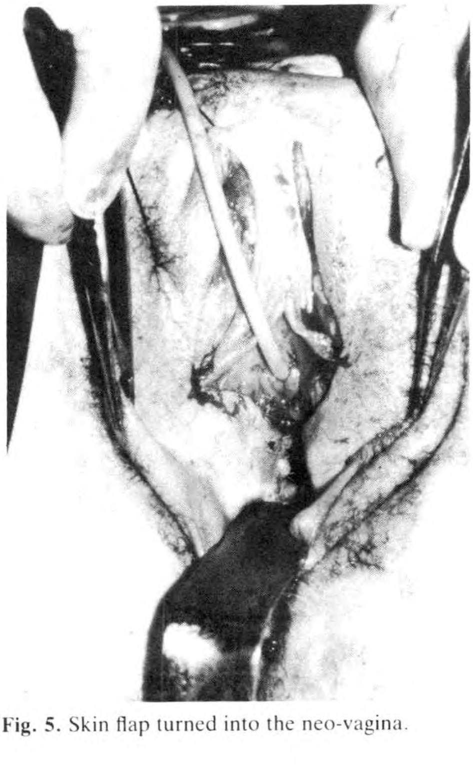

Fig. 5. Skin flap turned into the neo-vagina.

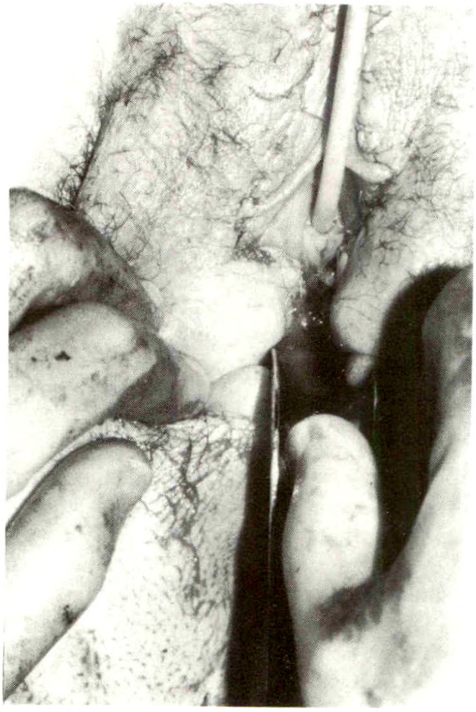

Fig. 6. Vulval appearance towards the end of the procedure.

wall. The abdominal skin was closed with subcuticular prolene and a suprapubic catheter was inserted into the bladder. Finally a large acroflavine pack was placed in the vagina.

The patient had a temperature of 37·5–38 °C for the first 3 days after surgery. Intravenous antibiotics were given and her temperature settled. When the acroflavine pack was removed after 4 days the skin flaps were viable and had adhered to the underlying tissue. The drains and suprapubic catheter were also removed at this stage. A week later examination under anaesthesia showed that the vagina was capacious and lined by non-hair-bearing healthy skin. The patient was prescribed oral contraceptives and is now having regular withdrawal bleeds. She has been advised to use a vaginal dilator once a day for 30 min for the first 3 months after the operation to prevent any slight tendency to vaginal contraction. Subsequent examination has shown that the vaginal patency and size has been maintained. The patient is not suffering from any untoward symptoms and is encouraged to know that she will be able to have a normal sex life and there is a reasonable chance that she will be fertile. Follow-up ultrasound scans have failed to demonstrate any abnormal pelvic pathology.

Discussion

Tissue expansion techniques, although established in other areas of the body (Argenta *et al.* 1983; Dickson *et al.* 1987), have not previously been attempted for vaginal reconstruction. The technique has proven entirely satisfactory in our patient although we had some misgivings before the operation. Tissue expanders are normally left *in situ* for approximately 3 months before definitive surgery. More rapid expansion was required in this case, as the patient was a young schoolgirl and could not afford to remain in hospital for a prolonged period. It would have been difficult for her to return to normal life with expanders *in situ* as the labial swellings were in contact medially and normal activities might have caused chafing. We were gratified therefore that considerable expansion could take place rapidly and that there was no tendency for contraction of the flaps. Clearly the labia are very distensible and this is borne out by anthropological investigations in the Kalahari Bushmen who practise tissue expansion techniques of the labia as a cultural ritual and achieve enormous enlargement in this way (Jeffreys 1972). Other similar areas which appear, from ritual techniques, to be amenable to considerable distension are the lip and ear lobes. Before the operation we were also concerned that the procedure might be painful, but because of the distensibility of this area there was very little discomfort. Other possible hazards were infection and haematoma formation. Blunt dissection lowers the chance of the latter whilst prophylactic antibiotic administration may be of value when implanting foreign material into this potentially infected area. The siting of the valve at considerable distance from the expanders themselves may have helped to reduce the chances of infection. Our patient remained in hospital throughout her treatment schedule, but it may be possible to teach patients to inflate their own expanders as out-patients. Intermittent expansion of each side might allow normal activities to continue as the problem of friction between the juxtaposed labial surfaces would be minimized.

The success of the procedure in this case will encourage us to use tissue expansion technqiues for other indications (Table 1). It is probable

Table 1. Common types of vaginoplasty and the conditions for which they are most suitable*

Procedure	Indication
Labial perineal flaps	Congenital adrenal hyperplasia
Amnion vaginoplasty, McIndoe split skin graft, devitalized bowel graft	Vaginal agenesis
Bowel pedicle	Cloacal anomalies
Williams' labial pouch	Stricture of vagina after radiotherapy
Vaginal pull through	Cloacal anomalies and partial vaginal agenesis. This operation will succeed when a small segment of vagina is absent. It is used in combination with a perineal flap for congenital adrenal hyperplasia where the vagina fuses with the urethra above the external sphincter

*None of these indications is absolute. Some authorities, for example, recommend the Williams' procedure or bowel pedicle for vaginal agenesis.

that this procedure will be most helpful in patients with cloacal anomalies, where the labia are typically small and do not provide enough tissue for a conventional flap, but where the upper vagina and cervix are normal. This technique will allow sufficient skin to be created for a large flap. Patients with cloacal anomalies are unsuitable for amnion vaginoplasty or other similar techniques because they frequently have stricturing from previous surgery and in some cases there may be concern that the mould could penetrate the nearby rectum. The tissue expanded flaps could be inserted in conjunction with bilateral ischiocavernosus flaps for construction of the perineal body (Elstein & Eyong 1986).

Future indications for tissue expansion vaginoplasty may include congenital adrenal hyperplasia where unsuccessful surgery has been attempted in infancy. It has become fashionable to carry out definitive vaginoplasty in infancy on patients with this condition (Hendren & Donahoe 1980). Few of these patients have reached puberty and if this operation is unsuccessful, then definitive treatment in later life will be more difficult, as the redundant labial skin which characterizes this condition will have been utilized. Techniques for creating further skin at the vaginal introitus might therefore be welcome. In addition, skin created in this way is mostly non-hair-bearing and therefore possibly preferable to that of conventional fasciocutaneous vulval flaps (Morton *et al.* 1986). The technique may also be useful in patients with traditional complete vaginal and Mullerian agenesis. This condition, which is much more common than partial Mullerian agenesis described in this paper, has been managed by non-operative methods, including the bicycle seat modification (Wharton 1938). Traditional surgical treatment consists of a procedure to achieve epithelialization of the vaginal space. All these techniques have disadvantages. The original McIndoe operation (McIndoe & Banister 1938) of partial thickness skin grafting has the further disadvantage of a disfiguring donor site. Devitalized bowel grafts involve intradominal surgery and intestinal resection. Amnion has recently been widely used for this purpose (Ashworth *et al.* 1986) but this is likely to become less popular as the spread of AIDS will make all procedures involving foreign tissue more hazardous. In addition all these techniques have the disadvantage that very rapid and complete stricturing will occur if deep, prolonged and repeated vaginal dilatation is not enthusiastically carried out. The tissue created by expansion techniques in the vulval area may also have uses apart from those of vaginal reconstruction. Thus, it may be helpful in some patients with large vesicovaginal fistulas or stricture after radiotherapy.

This case history shows that tissue expansion for the creation of vulval flaps is a potentially useful procedure. Analysis of congenital and acquired conditions of the vagina shows that it may have an important part to play in reconstructive gynaecological surgery.

Acknowledgments

We would like to thank Drs Rosemary Macdonald and Gordon Lyons for providing analgesia for transcutaneous inflation of the expander valves. Above all we would like to thank Sister Avril Harker and her staff for the

excellent and morale-building nursing care of this patient.

References

Argenta, L. C., Watanabe, M. J. & Grabb, W. C. (1983) The use of tissue expansion in head and neck reconstruction. *Ann Plast Surg* **11,** 31-37.

Ashworth, M. F., Morton, K. E., Dewhurst, J., Lilford, R. J. & Bates, R. G. (1986) Vaginoplasty using amnion. *Obstet Gynecol* **67,** 443-446.

Dickson, M. G., Sharpe, D. T., Dickson, W. A., Wilde, G. P., Brennan, T. G. & Roberts, A. H. N. (1987) Breast reconstruction by tissue expansion. *Ann R Coll Surg (Roy)* **65,** 18-22.

Elstein, M. & Eyong, E. (1986) Cloacal reconstruction and use of bilateral ischiocavernosus muscle flap for construction of the perineal body. Case report. *Br J Obstet Gynaecol* **93,** 402-406.

Hendren, W. H. & Donahoe, P. K. (1980) Correction of congenital abnormalities of the vagina and perineum. *J Pediatr Surg* **15,** 751-763.

Jeffreys, M. D. W. (1972) The onset of the menarche in the Negro—the Hottentot tablier. *Leech* **42,** 19-20.

McIndoe, A. H. & Banister, J. B. (1938) An operation for the cure of congenital absence of the vagina. *J Obstet Gynaecol Br Emp* **45,** 490-494.

Meldrum, D. R., Chang, R. J., Lu, J., Vale, W., Rivier, J. & Judd, H. L. (1982) 'Medical oophorectomy' using a long-acting GnRH agonist—a possible new approach to the treatment of endometriosis. *J Clin Endocrinol Metab* **54,** 1081-1083.

Morton, K. E., Davies, D. & Dewhurst, J. (1986) The use of the fasciocutaneous flap in vaginal reconstruction. *Br J Obstet Gynaecol* **93,** 970-973.

Wharton, E. A. (1938) A simple method of constructing a vagina. *Ann Surg* **107,** 842-854

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Candidiasis in women fitted with an intrauterine contraceptive device

WALTER PAREWIJCK, GEERT CLAEYS, MICHEL THIERY,
HENRY VAN KETS

Summary. Vaginal colonization by *Candida* spp. was compared in 117 women fitted with an intrauterine contraceptive device (IUCD users) and in 100 women not wearing an IUCD (control group). None of the subjects had factors currently assumed to predispose to yeast colonization or infection. Yeasts were present significantly more often in the IUCD users (20%) than in the control group (6%). In two of the 21 women with positive cultures the tail of the IUCD yielded substantially more colonies than the vaginal specimen and in seven, only the tail culture was positive. These findings strongly suggest that the IUCD is a predisposing factor in vaginal colonization by *Candida* strains. In half the women the presence of yeasts in the vagina was not associated with signs and symptoms of clinical infection. Of the 29 yeast strains isolated 17 were *C. albicans,* there was no difference in the prevalence of *C. albicans* between IUCD users and non-users or between symptomatic and asymptomatic women.

The occurrence of genital candidiasis in women seems to have increased during recent decades and many predisposing factors have been put forward to explain this trend (Odds 1979). The use of the intrauterine contraceptive device (IUCD) is not among these factors (Jacobson 1986), and a possible link between the IUCD and *Candida* colonization or infection does not seem to have been investigated previously.

This prospective study was undertaken in an attempt to fill that gap in our knowledge and answer two questions: does the IUCD enhance the carrier rate of *Candida* spp., and does the device predispose the wearer to acquire vaginal candidiasis?

Subjects and methods

The subjects were women who consulted their gynaecologist for the sole purpose of obtaining a routine check-up. None of those selected for microbiological investigation had any of the factors currently assumed to predispose to genital candidiasis such as pregnancy, diabetes, or the use of steroid contraception, and none had taken antibiotics or corticoid preparations during the previous 2 months. Women were also excluded from the study if they admitted to having more than one sex partner, had a partner believed to be sexually promiscuous, and if they practised oral or rectal sex.

Gent University Hospital, 185 De Pintelaan, 9000-Gent, Belgium

Department of Obstetrics
WALTER PAREWIJCK
MICHEL THIERY
HENRY VAN KETS

Department of Microbiology
GEERT CLAEYS

Correspondence: Professor M. Thiery, Vrouwenkliniek, Academisch Ziekenhuis, 185 De Pintelaan, 9000-Gent, Belgium

Of the 217 subjects included in the study, 117 were wearing an IUCD and they constituted the index group, the other 100 women did not wear an IUCD and they constituted the control group. For each subject we noted the presence or absence of signs or symptoms suggestive of genital candidiasis (vulvar itching, inflamed epithelia, vaginal discharge described as heavier than normal or found to be curdy on clinical examination).

Vaginal contents were sampled *in speculo* with a sterile cotton-tipped swab and the material was transferred to Nickerson agar. In most of the index group the marker thread of the IUCD was trimmed with sterile scissors and the fragment placed in a separate vial containing the same culture medium. After incubation, the presence of colonies was expressed semi-quantitatively. Brownish colonies were stained and transferred to Sabouraud agar to confirm the presence of yeast organisms. For differentiation, the yeast organisms were transferred to a culture medium (Rice cream agar) that triggers the development of chlamydospores only in *C. albicans*. Isolates not displaying chlamydospores were classed as other *Candida* strains.

For statistical analysis, the χ^2-test was used.

Results

Twenty-three IUCD wearers harboured yeast organisms in the vagina compared with six women in the control group, the difference was statistically significant ($P<0{\cdot}01$). Signs and symptoms suggestive of candidiasis were found in 14 women in the index group and in three in the control group, again the difference was statistically significant ($P<0{\cdot}01$).

Almost 50% of the IUCD users and 66% of the control subjects harbouring yeast organisms were asymptomatic (Table 1); thus, at least half the women with positive yeast cultures had no symptoms suggestive of candidiasis. One per cent of the total group had a negative culture but symptoms suggestive of candidiasis. In the women from whom only a few yeast colonies were isolated signs or symptoms were also found in about 50%, which suggests that the concentration of the vaginal yeast flora is not directly related to the clinical findings.

In 14 of the 21 women from whom samples from both the vagina and IUCD tail could be studied, both sets of cultures were positive and nine of these 14 women were symptomatic. In the other seven women only the tail of the IUCD yielded positive results and three of these women were symptomatic. It is notable that in two of the 14 women with positive cultures from both sources, fewer yeast colonies were obtained from the vagina than from the IUCD tail.

Seventeen of the 29 strains (59%) were identified as *C. albicans* (Table 2). The strain ratio (*C. albicans*/*Candida* spp.) was comparable for index and control subjects and was not influenced by the presence or absence of symptoms.

Discussion

The microbiological changes in the cervix and vagina have been thoroughly studied in women fitted with an IUCD (Davis 1968; Salmi *et al.* 1976; Corbishley 1977; Feichter *et al.* 1978; Goldacre *et al.* 1979; Persson *et al.* 1983; Kivijärvi *et al.* 1984; Peddie *et al.* 1984; Thiery *et al.* 1986) and the results indicate the greater prevalence of *Gardnerella vaginalis* and the bacterial vaginosis complex, *Actinomyces israelii* and

Table 1. Number of women with yeast organisms and signs or symptoms suggestive of candidiasis

	IUCD group (n = 117) n (%)	Non-IUCD group (n = 100) n (%)
Positive cultures	23 (20)	6 (6)
Signs/symptoms	14 (12)	3 (3)
Positive culture, symptomatic	12/23 (52)	2/6 (33)
Positive culture, symptomatic (few colonies)	5/12 (42)	1/2 (50)
Positive culture, asymptomatic	11/23 (48)	4/6 (66)
Negative culture, symptomatic	2/94 (2)	1/94 (1)

Table 2. Relation between yeast strain, presence of an IUCD, and clinical findings (number of patients)

	IUCD group (n = 117)		Non-IUCD group (n = 100)	
	C. albicans	Other strains	*C. albicans*	Other strains
Signs or symptoms	8	6	1	1
No signs or symptoms	5	6	3	1

some rather exotic species (*Eikenella*, *Capnocytophaga* and *Nocardia*). In most of these studies yeast organisms received slight or no attention. Authors who took their presence into account usually failed to find an association between *Candida* colonization/infection and IUCD use (Davis 1968; Corbishley 1977; Goldacre *et al.* 1979), but Kaufmann (1985) reported a lower prevalence of *Candida* on the device than in the vagina. This lack of interest in yeasts is the more surprising because we know that in other cavities such as the mouth, *C. albicans* carriage is enhanced by the wearing of dentures (Tapper-Jones *et al.* 1981). Furthermore, many a gynaecologist must have observed an occasional patient whose troublesome recurrent candidiasis was apparently cured by removal of the IUCD. The results of the present study confirm the clinical impression that the IUCD predisposes to colonization and infection by *C. albicans* or other yeast strains. However, only half the women in whom yeast organisms were detected were symptomatic and in most of them the signs and symptoms were mild and definitely not the main reason for their consulting a physician. As in vaginitis with other aetiologies, the clinical symptoms associated with a yeast infection lacked specificity and cultures were negative in a minority of the symptomatic patients.

The design of this study does not allow us to draw conclusions as to whether the association between IUCD use and the presence of yeast organisms is a causal one. That is, we do not know whether this foreign body is the cause of vaginal colonization by *Candida* spp. or if the association is an expression of other differences between the index and control populations. However, because other associated factors known to predispose to yeast infection were eliminated, we may assume that index and control cases were satisfactorily matched except for one factor, i.e. the presence of an IUCD. Why an IUCD predisposes the wearer to colonization by yeasts is not known, but one finding—that yeast organisms are more prevalent on the IUCD than on the vaginal mucosa—tends to favour the assumption that the tail of the device acts as a reservoir and thus prevents the mucosa from clearing itself of yeast organisms.

More than half the strains cultured from the vagina were *C. albicans*. Because there was no difference in the prevalence of *C. albicans* either between IUCD users and non-users or between symptomatic and asymptomatic women, we do not feel entitled to conclude that this species has greater pathogenicity or virulence than other yeast strains.

References

Corbishley, C. M. (1977) Microbial flora of the vagina and cervix. *J Clin Pathol* **30,** 745-748.

Davis, B. A. (1968) Vaginal moniliasis in private praxis. *Obstet Gynecol* **34,** 40-45.

Feichter, G. E., Nohlen, M. & Tauber, P. F. (1978) Bakterieller Fluor bei intrauteriner Kontrazeption. *Fortschr Med* **37,** 1938-1940.

Goldacre, M. J., Watt, B., Loudon, N., Milne, L. J. R., Loudon, J. D. O. & Vessey, M. P. (1979) Vaginal microbial flora in normal young women. *Br Med J* **i,** 1450-1453.

Jacobson, J. B. (1986) Current thinking on the pathogenesis of vulvovaginal candidiasis. *J Reprod Med* **31,** 645-646.

Kaufmann, E. (1985) Etude d'ensemble des différents germes responsables de salpingite et de leur incidence lors d'une étude bactériologique prospective en série continue chez des porteuses de stérilet. *Méd Hyg* **43,** 1863-1873.

Kivijärvi, A., Järvinen, H. & Grönroos, M. (1984) Microbiology of vaginitis associated with the intrauterine contraceptive device. *Br J Obstet Gynaecol* **91,** 917-923.

Odds, F. C. (1979) *Candida and Candidosis.* Leicester University Press, Leicester.

Peddie, B. A., Bishop, V., Bailey, R. R. & McGill, H. (1984) Relationship between contraceptive method and vaginal flora. *Aust NZ J Obstet Gynaecol* **24,** 217-218.

Persson, E., Holmberg, K., Dahlgren, S. & Nilsson, L. (1983) *Actinomyces israelii* in the genital tract of women with and without intra-uterine contraceptive devices. *Acta Obstet Gynecol Scand* **62,** 563-568.

Salmi, T., Järvinen, H., Rauramo, L. & Timonen, H. (1976) Cervical bacterial flora in women fitted with a copper-releasing intra-uterine contraceptive device. *Acta Obstet Gynecol Scand* **55,** 317-320.

Tapper-Jones, L. M., Aldred, M. J., Walker, D. M. & Hayes, T. M. (1981) Candidal infections and populations of *Candida albicans* in mouths of diabetics. *J Clin Pathol* **34,** 706-711.

Thiery, M., Claeys, G., Mrozowski, B., Van Den Broecke, R., Van Kets, H., Parewijck, W., Derom, R., Defoort, P. & Vanlancker, M. (1986) Significance of colonization of the lower female genital tract with *Actinomyces israelii*. *IRCS Med Sci* **14,** 292-293.

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Management of a bleeding aberrant cervical artery following vacuum suction termination. Case report

S. K. S. CHORDIA

Case report

A 29-year-old married woman was referred for consideration of termination of pregnancy and a request for laparoscopic sterilization. She had had one stillbirth followed by two live births 5 and 2 years previously. She also had had an uncomplicated vaginal termination a year ago. Clinical and ultrasound examination showed that she was at 12 weeks gestation. It was decided that the pregnancy could be terminated under Grounds II and III of the Abortion Act (1967). Sterilization was also agreed as this was her fifth pregnancy and her husband had been on the waiting list for a vasectomy 1 one year.

At vaginal termination a 12-week pregnancy was removed using a 10-mm Karman and up to 400 mmHg of vacuum pressure after dilating the multiparous os to the size of a Hegar's 9 dilator. The blood loss was estimated to be less than 100 ml. Laparoscopic sterilization was carried out using two Filshie clips on each fallopian tube. The pelvic organs appeared normal.

One hour later there was moderate haemorrhage from the vagina and the uterus felt lax. Her blood pressure was 100/60 mmHg and her pulse was 104 beats/min. Intravenous ergometrine, 0·5 mg, was given and an intravenous infusion of 500 ml of Hartmann's solution containing 100 units of oxytocin was given at 60 drops/min for 10 min. There was no reduction in her vaginal bleeding and the blood loss was estimated to be 700 ml. Blood transfusion was started and the patient was taken back to the theatre with a suspected injury to the uterus.

Bearing in mind the proximity of the ureters a sponge forceps was applied short of the internal os to the left side of the cervix as shown in Fig. 1. The bleeding was from the left side of the cervical canal. At repeat laparoscopy there was no evidence of a uterine perforation or a broad ligament haematoma. The uterus had not increased in size. In view of the patient's age it was decided not to perform a hysterectomy and that a less invasive procedure should be undertaken in the form of repair from the vaginal route. The sponge forceps was removed but this led to further bleeding and it was reapplied.

The patient was catheterized and the vaginal wall was opened by a transverse incision, as in an anterior repair; the bladder was then reflected and pushed up to make sure the ureters were out of the way. The left side of the cervix was cut open with scissors, in stages, short of the internal os. An aberrant branch of the cervical artery was seen bleeding just beyond the cut edge arising from the inner wall of the cervix and protruding into the canal (Fig. 2). There was no evidence of a perforation or any other damage to the uterus or the cervix. Both ends of the damaged and bleeding artery were clamped and ligated using 'O' chromic catgut. Haemostasis was complete. The cervix and vaginal walls were repaired with chromic 'O' catgut. Total blood loss was estimated to be 1200 ml. This was replaced by four units of cross-matched blood. A Foley's catheter and a vaginal pack were used for 12 h. The patient was treated with cephradine, 500 mg four times a day, given intramuscularly initially then orally for 7 days, and metronidazole, 100 ml intravenous infusion in 2 h initially then oral tablets, 200 mg three times a day for 7 days. The patient made an uneventful recovery and was discharged 48 h later. She was advised to rest for 2 weeks and abstain from sexual intercourse for 6 weeks. During the entire postoperative period she had no further problems. At 6 weeks follow-up the pelvic organs were within normal limits and the vaginal and cervical wounds had healed.

Discussion

A literature search by computer did not reveal any other recorded case of diagnosis and treat-

144 Harley Street, London W1N 1AH
S. K. S. CHORDIA *Private Consultant Gynaecologist*

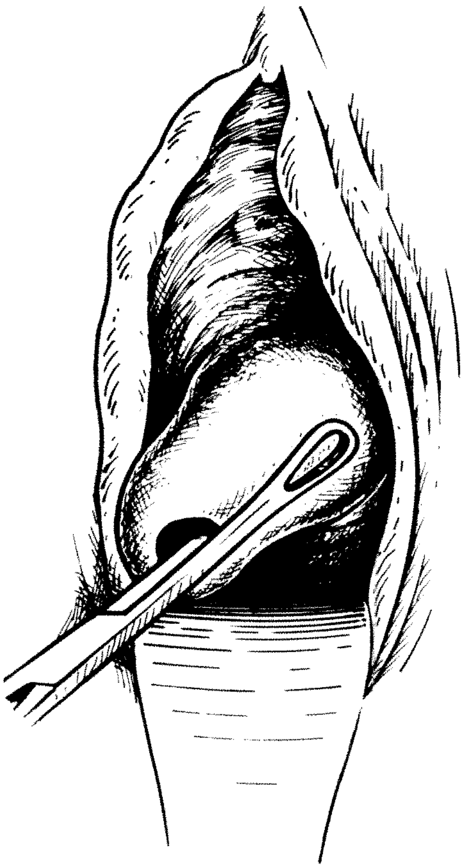

Fig. 1. The application of sponge forceps to the left cervical angle.

ment of a damaged aberrant artery in the cervical canal during vaginal termination of pregnancy, which did not result in a hysterectomy. Lowensohn & Hibbard (1974) reported four patients who required hysterectomies after abortion, in two of them unsuccessful attempts had been made to control haemorrhage by deep cervical sutures. Deere & Jacobs (1963) and Mullins *et al.* (1979) reported postabortal abdominal ligation of the uterine arteries, and Ross (1965) reported transvaginal ligation of the uterine arteries following caesarean section. In my patient it is suggested that a cervical tear either during previous childbirth or at a previous termination of pregnancy exposed one of the branches of the left cervical artery. In the first report of the Joint Program for the Study of Abortion (JPSA) the rate of pre-existing complications averaged 4·2% for all abortions, and increased with age, parity, marital status and gestational age (Tietze & Lewit 1972). In my patient the aberrant artery lay exposed in the cervical canal and was damaged by the Karman catheter during the abortion procedure.

Whenever the operator is faced with an unexpected haemorrhage after vaginal termination of pregnancy a laparoscopic examination should be made to exclude uterine perforation or a broad ligament haematoma. If no cause is found then the application of sponge forceps on either one or both lateral cervical angles (Fig. 1) will help to locate the site of the aberrant artery in the cervical canal. Care should be taken not to damage the ureters. Bleeding from an aberrant artery in the cervical canal cannot be detected by laparoscopy or laparotomy, or by a hysteroscope in the presence of large amounts of blood, and repair by the abdominal route is very difficult.

Vaginal repair as described in my patient can prevent unnecessary hysterectomy with its consequent physical and mental trauma. There is the added advantage of a shorter stay in hospital.

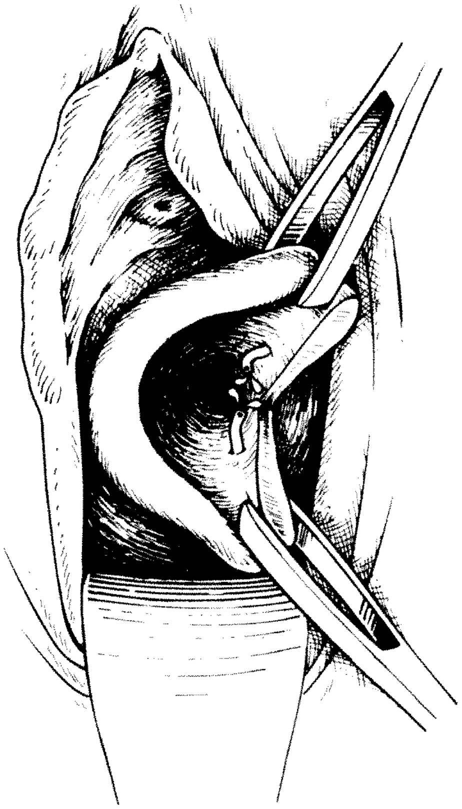

Fig. 2. The cervical cut on the left and the spurting aberrant cervical artery just beyond the cut edges arising from the inner wall of the cervix.

Such patients, in future pregnancies, should have an elective caesarean section.

Acknowledgments

I thank Dr Thikra Bashir, Consultant Gynaecologist, Cuckfield Hospital, Dr Rex Binning for their advice, and Sareeta for her help. I am grateful to Mrs Anne Wadmore (Department of Medical Illustration, Westminster Hospital Medical School, London) for preparing these difficult illustrations, and Mrs Joan Godfrey for her help with them. I also thank Miss Patricia Want (Librarian, RCOG) for the help with the search of references.

References

Deere, J. & Jacobs, W. (1963) Profuse uterine haemorrhage associated with septic incomplete abortion managed by ligation of uterine arteries. *Am J Obstet Gynecol* **86**, 136-137.

Lowensohn, R. I. & Hibbard, L. T. (1974) Laceration of the ascending branch of the uterine artery: a complication of therapeutic abortion. *Am J Obstet Gynecol* **118**, 36-38.

Mullins, J. H. Jr, O'leary, J. A. & Askel, S. (1979) Uterine artery ligation for postabortal haemorrhage. *Obstet Gynecol* **54**, 383-384.

Ross, I. C. (1965) Ligation of uterine arteries, per vagina, in a case of recurrent secondary postpartum haemorrhage following cesarean. *Aust NZ J Obstet Gynaecol* **5**, 215-218.

Tietze, C. & Lewit, S. (1972) Joint Program for the Study of Abortion (JPSA)—Early medical complications of legal abortion. *Stud Fam Plann* **3**, 97-122.

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Verrucous carcinoma of the vulva containing human papillomavirus-11. Case report

M. E. CROWTHER, J. H. SHEPHERD, C. FISHER

Case report

A 25-year-old woman presented in November 1985 with a rapidly growing vulval lesion (Fig. 1). Vulval condylomata, present since 1977, had recurred in spite of cautery and podophyllin therapy. She also had a 2-year history of a recurrent right-sided Bartholin's abscess and warty invasion of this site began 11 months before presentation. Biopsies had shown 'papillomatosis, acanthosis and koilocytosis without evidence of anaplasia'. Various treatments elsewhere with cautery, interferon, 13 cis-retinoic acid, intralesional bleomycin and local excision had been unsuccessful.

In 1982 she was noted to be anaemic with a neutropenia, and a diagnosis of myelodysplasia was made but no specific treatment was given.

On examination, the right side of the vulva was replaced by a 15 × 10 cm malignant-looking warty lesion with papilliferous fronds which extended from the mons pubis onto the inner aspect of the thigh, and the lower third of the vagina on the right. It was clear of the external urethral meatus and clitoris. A large sinus track extended from the right buttock to the right ischiorectal fossa and tuberosity, and a second sinus track went from the right labium majus across the inner thigh. There were no palpable lymph nodes. Pelvic examination was normal.

The haemoglobin level was 9·2 g/dl and white cell count $3{\cdot}4 \times 10^9$/l with 62% neutrophils and 16% lymphocytes. The T-helper/suppressor cell ratio was 0·7 (normal >1·7). Bone marrow was myelodysplastic with abnormal granulopoiesis but normal erythroid progenitor cells.

On 2 December 1985, the patient underwent a radical vulvectomy, bilateral groin lymphadenectomy and wide excision of tumour from the vagina, inner thigh and right ischiorectal fossa. Primary closure of the vulvectomy wound was possible on the left side but a rectus muscle myocutaneous flap was grafted into the defect on the right (Fig. 2).

The histological diagnosis confirmed the clinical suspicion of verrucous carcinoma (Fig. 3). The lesion was papillomatous and mostly exophytic with numerous frond-like outgrowths of well-differentiated squamous epithelium. The tumour was broadly based with blunt, rounded processes pushing into the dermis with a focal inflammatory reaction. The cells showed minimal atypia but many had cytoplasmic vacuolation. Lymph nodes were negative and the margins were clear.

DNA hybridization studies revealed the presence of large amounts of the HPV-11 genome in the lesion and surrounding healthy tissue (Fig. 4).

Her postoperative recovery was uneventful and the graft healed well. When seen 3 months after the operation, she had two warty lesions around the urethral meatus, excision biopsy of which showed condylomata acuminata. She remains disease free 20 months after surgery. Her prognosis should be good. She has a functional vagina and the plastic repair of the vulva is very acceptable to her.

Discussion

The aetiology of verrucous carcinoma is not known although poor hygiene and chronic infection have been implicated (Ackerman 1948;

The Royal Marsden Hospital, London SW3
Department of Gynaecological Oncology
M. E. CROWTHER *Gynaecological Oncology Fellow*
J. H. SHEPHERD *Consultant Gynaecological Oncologist*

Department of Histopathology
C. FISHER *Consultant Histopathologist*

Correspondence: J. H. Shepherd, Consultant Gynaecological Oncologist, St Bartholomew's Hospital, West Smithfield, London EC1A 7BE

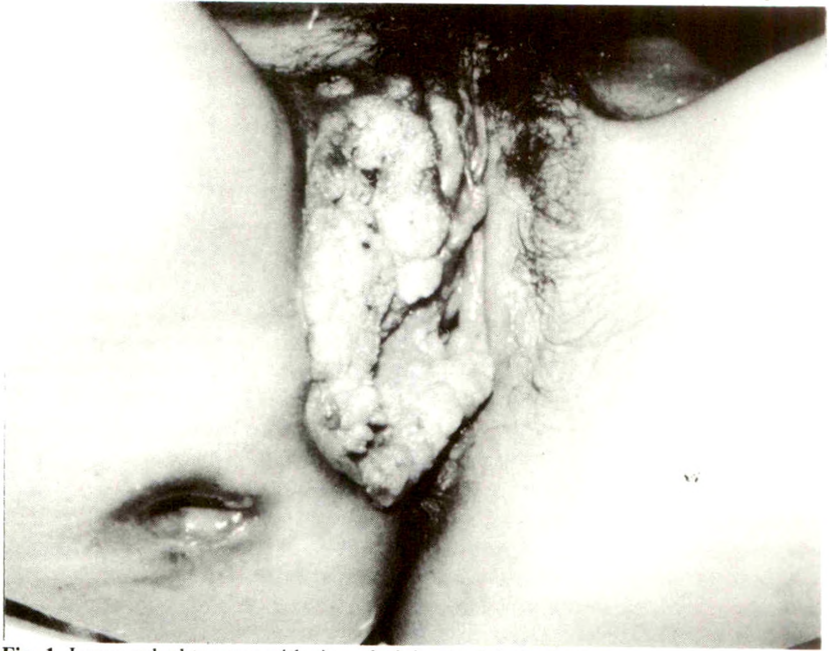

Fig. 1. Large vulval tumour with sinus draining to right buttock.

Kraus & Perez-Mesa 1966). Although a third of all the reported cases of vulval verrucous carcinoma have had genital warts (Crowther *et al.* 1988), the relation to other sexually transmitted diseases such as syphilis is not clear. This patient had had recurrent warts for 8 years, but she also had myelodysplasia, and immunosuppression increases susceptibility to genital warts and perhaps also to malignant change (Shokri-Tabibzadeh *et al.* 1981).

Although the role of human papillomavirus (HPV) in the aetiology of genital warts is increasingly recognized (Gissman *et al.* 1982), its association with verrucous carcinoma is not

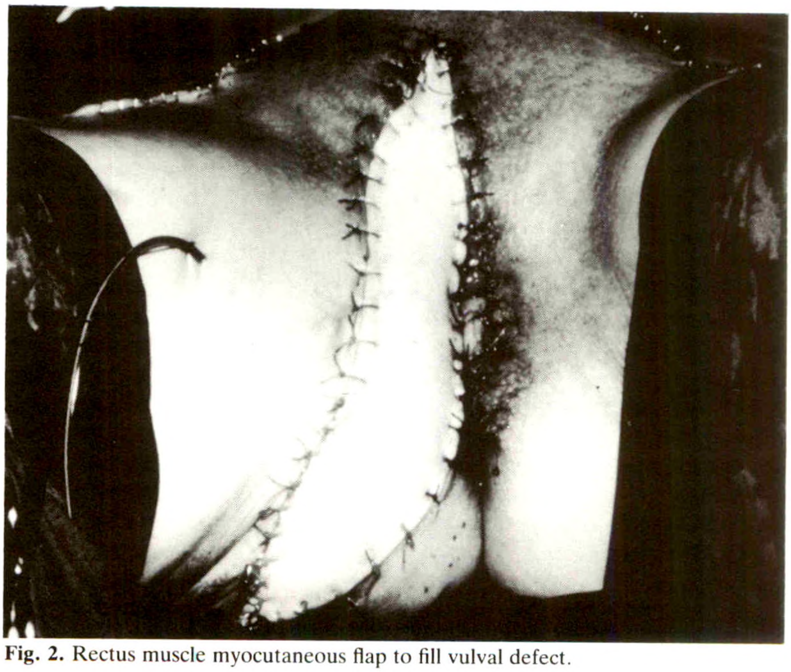

Fig. 2. Rectus muscle myocutaneous flap to fill vulval defect.

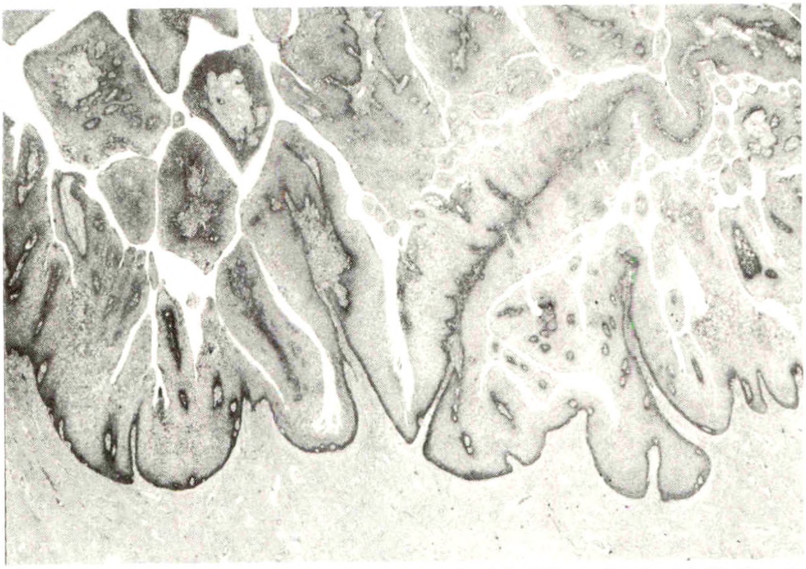

Fig. 3. Verrucous carcinoma with exophytic growth, well-differentiated epithelial fronds and blunt downward extensions demarcated from dermis (haematoxylin and eosin × 60).

clear. HPV has been detected in some lesions, the commonest type being HPV-6 (Table 1). This is, however, the first report of the presence of HPV-11 in a verrucous carcinoma, a virus considered to be 'low risk' for malignant change. The decreased immunity of this patient may have predisposed her to infection with this virus but whether its presence will predispose her to recurrent disease is not clear at this stage. Diagnosis of these tumours may be difficult and confusing. Lesions are often misdiagnosed as benign condylomata yet the clinician is faced with a fungating, invasive tumour which looks anaplastic. Conversely it may be called atypical squamous cell carcinoma. Correct diagnosis is important. If the tumour is underdiagnosed as a condyloma acuminatum, treatment with laser, cautery or podophyllin will be inappropriate as in this case, where the growth accelerated in spite of therapy. If on the other hand the tumour is overdiagnosed as a squamous cell carcinoma, radiotherapy may well be instituted and result in anaplastic change in the verrucous carcinoma (Ackerman 1948; Kraus & Perez-Mesa 1966).

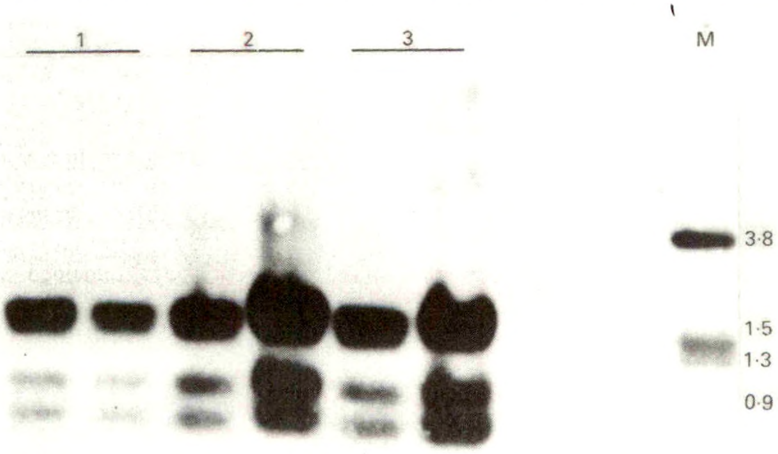

Fig. 4. Autoradiograph of total DNA extracted from (1) the edge, (2) the centre of the lesion, and (3) the resected margin. The DNA was digested with Pstl, hybridized, and linear 32 P labelled HPV-6 DNA and HPV-11 DNA detected in all three areas.

Table 1. Human papillomavirus associated with verrucous carcinoma of the vulva

Reference	Site	Human papillomavirus type (method of detection)
Ubben *et al.* (1979)	Vulva, anus	Type not stated (electron microscopy and hybridization)
Okagaki (1981)	Vulva	HPV particles 45–50 nm in size (electron microscopy)
Gissman *et al.* (1982)	Not stated	HPV-6a, HPV-6b (Southern blot hybridization)
Zachow *et al* (1982)	Vulva, penis	Integrated HPV-DNA in vulva, HPV-6 in penis (Southern blot hybridization)
Rando *et al.* (1986)	Vulva	HPV-6b (hybridization)
Crowther *et al.* (1988)	Vulva	HPV-11 (hybridization)

There are discriminatory features between these lesions (Crowther *et al.* 1988). The verrucous carcinoma is single, large and expanding, unlike the small, exophytic condylomata acuminata. There is minimal cellular atypia compared with a well-differentiated squamous cell carcinoma where increased mitotic activity and abnormal cellular maturation is seen. The major histological clues (Table 2) are the well-differentiated bulbous rete pegs pushing into the stroma and the intact basement membrane. Large and deep biopsies are thus mandatory. The best diagnostic guide is the clinical behaviour of the tumour, particularly its failure to respond to conservative treatment. Diagnosis requires close collaboration between the clinician and pathologist.

This patient was very young, the average age for women with vulval verrucous carcinoma being 59 years (Crowther *et al.* 1988). The treatment of choice is wide local excision or radical surgery for a large or recurrent lesion, and this is curative in over 60% of cases. Chemotherapy (Vayrynen *et al.* 1981), podophyllin and radiotherapy are not helpful, and a simple vulvectomy is more likely to be followed by recurrence. The prognosis for vulval tumours appears to be good and death is from local spread to the bladder and rectum or metastatic disease from squamous cell carcinoma (Gallousis 1972; Vayrynen *et al.* 1981).

Table 2. Histological criteria for the diagnosis of verrucous carcinoma

1 Papillary projections have no fibrovascular core
2 Hyperkeratosis
3 Intact basement membrane
4 Very few mitotic figures and mild epithelial atypia
5 'Pushing' border but no infiltration of cells into stroma
6 Dense inflammatory reaction
7 Sharp transition between lesion and normal epithelium

Verrucous carcinoma itself is rarely associated with metastatic disease and many reports of such spread show histological evidence of nests of squamous cell carcinoma invading the stroma beneath the tumour (Crowther *et al.* 1988). However, it is not clear whether many verrucous carcinoma, if examined carefully histologically, will be found to have small areas of invading squamous cell carcinoma within them. For this reason alone, surgical excision should be adequate and include lymph nodes (Gallousis 1972). If invading cells are found, the lesion should be considered a separate entity with a different biological behaviour that predisposes to recurrence and metastatic spread.

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References

Ackerman, L. V. (1948) Verrucous carcinoma of the oral cavity. *Surgery* **23**, 670-678.

Crowther, M E., Shepherd, J. H. & Lowe, D. (1987) Verrucous carcinoma in the female genital tract. a review of 102 cases. *Obstet Gynecol Surv* (In press).

Gallousis, S (1972) Verrucous carcinoma Report of three vulvar cases and review of the literature. *Obstet Gynecol* **40**, 502-507.

Gissman, L., De Villiers, E. M. & Zur Hausen, H. (1982) Analysis of human genital warts (condylomata acuminata) and other genital tumors for human papillomavirus type 6 DNA. *Int J Cancer* **29**, 143-146

Kraus, F. T & Perez-Mesa, C. (1966) Verrucous carcinoma. Clinical and pathologic study of 105 cases involving oral cavity, larynx and genitalia. *Cancer* **19**, 26-38.

Okagaki, T. (1981) "Warty carcinoma" of the vulva: a probable implication of human papilloma virus as the causative agent. *Lab Invest* **44,** 49A.

Rando, R. F., Sedlacek, T. V., Hunt, J., Jenson, A. B., Kurman, R. J & Lancaster, W. D. (1986) Verrucous carcinoma of the vulva associated with an unusual Type 6 human papillomavirus. *Obstet Gynecol* **67,** 70S-75S.

Shokri-Tabibzadeh, S., Koss, L. G., Molnar, J. & Romney, S. (1981) Association of human papillomavirus with neoplastic processes in the genital tract of four women with impaired immunity *Gynecol Oncol* **12,** S129-140.

Ubben, K., Krzyzek, R., Ostrow, R., Bender, M , Zelickson, A., Faras, A. & Pass, F. (1979) Human papillomavirus DNA detected in two verrucous carcinomas. *J Invest Dermatol* **72,** 195.

Vayrynen, M., Romppanen, T., Koskela, E., Castren, O. & Syrjanen, K. (1981) Verrucous squamous cell carcinoma of the female genital tract. Report of three cases and survey of the literature. *Int J Gynaecol Obstet* **19,** 351-356.

Zachow, K. R., Ostrow, R S., Bender, M., Watts, S., Okagaki, T., Pass, F. & Faras, A. J. (1982) Detection of human papillomavirus DNA in anogenital neoplasias. *Nature* **300,** 771-773

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SHORT COMMUNICATIONS

The management of severe disseminated intravascular coagulopathy complicating placental abruption in the second trimester of pregnancy

Karl S. Oláh *Acting Registrar,* Harry Gee *Senior Lecturer* & Peter G. Needham *Consultant, Department of Obstetrics and Gynaecology, Selly Oak Hospital, Raddlebarn Road, Selly Oak, Birmingham B29 6JD*

Monteiro *et al.* (1987) reported a patient with placental abruption associated with severe disseminated intravascular coagulation (DIC) in the second trimester of pregnancy. Placental abruption at this stage of pregnancy is uncommon but, as the case illustrated, the associated DIC can be life threatening and out of proportion to the degree of placental separation. Termination of the pregnancy may become necessary to halt the consumptive coagulopathy (Sher & Statland 1985), but in the presence of a severe progressive coagulopathy, the method employed at this gestation would require careful consideration.

We would like to report a similar case, in which a life-threatening DIC resulted from a placental abruption in the second trimester, with survival of the fetus. The patient, a 20-year-old white Caucasian, was admitted at 19 weeks gestation with vaginal bleeding. On examination the patient was cardiodynamically stable, with minimal vaginal loss. The uterus was hard and tender but of appropriate size for her dates An ultrasound scan showed a viable fetus and a fundally implanted placenta There was no evidence of any retroplacental clot. On admission, vaginal blood loss became severe. Tissue was passed, and this was later shown histologically to be fibrin Clotting studies revealed a severe DIC, with a prothrombin time of 3·9 s, a partial thromboplastin time of 96 s (control 43 s), serum fibrinogen of 0·097 g/dl, fibrin degradation products of >1000 µg/ml and platelets of 88 × 10^9/l. Within 24 h the haemoglobin dropped from 12·6 g/dl to 6·7 g/dl There was no evidence of haemolysis. However, despite an initial severe haemorrhage, the bleeding ceased with conservative management (fresh whole blood, fresh frozen plasma and cryoprecipitate) within 24 h, and within 48 h the coagulation factors had returned to normal. The fetus had remained alive throughout the above events, and repeat ultrasound scan showed a normal fetus and placenta. Subsequently, there was 'spotting' of blood at 20 weeks and again at 22 weeks. However, at 26 weeks gestation the onset of persistent heavy vaginal bleeding with the onset of uterine contractions necessitated delivery An 870 g male infant was born by caesarean section with Apgar scores of 7 at 1 min, and 10 at 5 min Although requiring special care facilities, the baby made good progress and was subsequently discharged from the unit.

It is apparent that the coagulopathy induced in our patient, and in the one reported by Monteiro *et al.* (1987), is out of proportion to the degree of placental separation. A large placental separation in the third trimester would lead to fetal death, and would be detectable ultrasonically as a transonic area between the basal layer of the placenta and the uterine wall (Grannum 1983). Thus, assuming that the area concerned is small, the disruption and release of thromboplastins from the placenta at this gestation must be considerably greater than that in the third trimester. In addition, even though a severe DIC developed rapidly, the tendency appears to be for complete resolution of the coagulopathy to occur. This would further reinforce the view of Monteiro *et al* (1987) that cautious conservative management is indicated in such a case as long as the fetus is alive, and after careful consideration of the well-being of the woman

References

Grannum, P A (1983) Ultrasound examination of the placenta *Clin Obstet Gynaecol* **10**, 459-473

Monteiro, A A , Inocencio, A C & Jorge, C S

(1987) 'Placental abruption' with disseminated intravascular coagulopathy in the second trimester of pregnancy with fetal survival Case report. *Br J Obstet Gynaecol* **94**, 811-812

Sher, G & Statland, B E (1985) Abruptio placenta with coagulopathy: a rational basis for management *Clin Obstet Gynecol* **28**, 15-23

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Angiotensin-converting enzyme inhibitors during pregnancy: a survey of 22 patients given captopril and nine given enalapril

Carmen Kreft-Jais *Département de Pharmacologie Clinique, Hôpital Broussais, Paris,* Pierre-Francois Plouin *Service d'Hypertension Artérielle, Hôpital Broussais, Paris,* Catherine Tchobroutsky *Maternité du Port Royal, Paris* & Marie-Jeanne Boutroy *Service de Médecine Néonatale, Maternité Régionale Universitaire, Nancy, France*

Inhibition of the maternal renin system with angiotensin-converting enzyme (ACE) inhibitors may affect fetal growth or survival through alterations in placental perfusion. Thus, administration of captopril to pregnant rabbits or large doses of enalapril to pregnant ewes increases the rate of stillbirths (Broughton-Pipkin & Wallace 1986). Moreover, the fetal renin system can also be inhibited with consequent alterations in systemic and renal haemodynamics, since captopril (Boutroy *et al.* 1984) and enalapril (J. Nussberger, personal communication) have been shown to decrease fetal ACE activity in man. Among 15 reported pregnancies treated with captopril, either alone or in association with a diuretic, there was one stillbirth and two neonatal deaths due to anuria, the others had favourable outcomes (Plouin & Tchobroutsky 1985) From a survey of pregnancies exposed to ACE inhibitors we describe 31 further pregnancies of which 22 were exposed to captopril and nine were exposed to enalapril.

Patients, methods and results

This survey was organized through the Société pour l'Etude de l'Hypertension au cours de la Grossesse and publicized at local meetings and in the medical press. Physicians in charge of pregnant patients given ACE inhibitors were invited to contact us by phone. They were reminded that these drugs carry potential risks to the fetus and are not indicated in pregnancy. In all cases, however, prescription had either preceded conception or had been justified by severe maternal hypertension, unresponsive to regular treatment. Whether captopril or enalapril treatment was maintained or not, pertinent maternal and perinatal data were collected by mailed questionnaires, and contact with the physicians concerned was maintained by phone or mail for up to 1 month after the end of the pregnancy.

Thirty-four pregnancies were reported between June 1985 and December 1986, including three terminated by induced abortion, but without histological study. Table 1 summarizes data from the 31 remaining pregnancies. Twenty-one women conceived while they were taking ACE inhibitors and in 15 women therapy continued until the end of pregnancy. Most women (27 of 31) had chronic essential or renal hypertension, and three were proteinuric before pregnancy (patients 11, 24 and 25). Proteinuria of $\geq$1 g/24 h developed during pregnancy in another five patients. Two of the pregnancies exposed to enalapril miscarried. Two fetal deaths occurred with captopril and one with enalapril, all three were associated with severe proteinuric hypertension Preterm delivery occurred in 11 women given captopril and in one given enalapril, all of them were delivered by caesarean section before labour. Six of the 26 liveborn babies were small for gestational age, four were in the captopril-treated and two in the enalapril-treated group. Seven women who had taken captopril or enalapril throughout pregnancy were delivered of liveborn babies. Perinatal outcome in the six pregnancies treated with ACE inhibitors in combination with diuretics was unremarkable. Two preterm infants born to women given captopril until delivery had a patent ductus arteriosus, requiring surgical repair in patient no. 7 after failure of attempted closure with indomethacin.

Table 1. Maternal disease, highest recorded diastolic blood pressure (DBP) during pregnancy, dosage and duration of treatment with angiotensin-converting enzyme inhibitor (ACEI) Unless mentioned, infants were alive 28 days after birth

ACEI	Patient no	Aetiology of hypertension	Highest DBP (mmHg)	Exposure to ACEI		Gestational age at birth (weeks)	Birthweight (g)	Remarks
				Dose (mg/day)	During weeks			
Captopril								
	1	Pre-eclampsia	120*	150	25–29	29	700	Stillbirth
	2	Pre-eclampsia	150*	200	29–31	31	1240	Respiratory distress, patent ductus arteriosus
	3	Essential	130	75	29–32	32	900	
	4	Essential	120*	25	10–11	33	1610	
	5	Pre-eclampsia	120*	100	28	34	1450	Stillbirth
	6	Essential	110	150	0–34	34	1550	Altizide 15 mg/day + spironolactone 25 mg/day 0–34 weeks
	7	Pre-eclampsia	120*	75	32–35	35	1460	Patent ductus arteriosus
	8	Essential	100	100	0–35	35	1840	
	9	Essential	130	100	0–7	35	2460	Tienilic acid 250 mg/day 0–7 weeks
	10	Essential	130	100	17–36	36	2670	
	11	Glomerulopathy	100*	50	0–36	36	2140	Triamterene 100 mg/day 0–36 weeks
	12	Essential	130	75	20–37	37	2640	
	13	Essential	120	50	0–8	37	3050	
	14	Uropathy	80	150	0–10	37	2250	
	15	Essential	100	100	0–10	38	3360	Altizide 15 mg/day + spironolactone 25 mg/day 0–10 weeks
	16	Essential	110	50	0–9	38	3000	
	17	Essential	130	100	34–38	38	2500	
	18	Essential	80	100	0–39	39	4180	Furosemide 20 mg/day 21–37 weeks
	19	Essential	90	100	0–39	39	2750/3000 (twins)	
	20	Essential	85	25	0–10	40	3380	
	21	Essential	120	50	0–15	40	3360	
	22	Unclassified	100	50	0–41	41	3850	
Enalapril								
	23	Essential	98	20	0–7	7	—	Miscarriage, 44-year-old woman
	24	Essential	120*	20	0–6	11	—	Miscarriage, 41-year-old diabetic
	25	Glomerulopathy	120*	30	24–26	26	600	Stillbirth
	26	Lupus	80	10	0–7	36	2525	Prednisone 30 mg/day throughout pregnancy
	27	Essential	80	20	0–28	37	3250	
	28	Essential	80	20	0–7	38	3550	
	29	Essential	120	20	0–4	38	2380	
	30	Essential	105	20	0–40	40	2260	Furosemide 40 mg/day 0–35 weeks
	31	Essential	70	10	0–7	41	3800	

*Proteinuria ≥1 g/24 h during pregnancy.

Comment

This survey, based on spontaneous reports, does not allow an estimation of the frequency of the prescription of ACE inhibitors during pregnancy in France. Also we cannot compare the frequency of morbid events associated with captopril or enalapril therapy with those reported for drugs approved for treating hypertension in pregnancy; most of the women in the present series were treated with ACE inhibitors because conventional drugs, used as a first line treatment, had failed to control their blood pressure. In this selected group of high-risk pregnancies, severity of maternal disease or consequent obstetrical decisions, as well as ACE inhibitors, could account for fetal death or growth retardation, preterm delivery, and patent ductus arteriosus. With these restrictions in mind, a few qualitative observations can be made.

The absence of malformation in the 14 pregnancies exposed to captopril in the first trimester cannot rule out the possibility of a teratogenic effect. The possible malformation reported from South Africa by Duminy & Burger (1981) remains, however, the only suspected case. Pregnancies exposed to captopril or enalapril had similar fetal and neonatal outcomes. Despite a limited transplacental transfer in the ewe (Broughton-Pipkin & Wallace 1986) and the optimistic results of an uncontrolled study in human pregnancy (Scanferla *et al.* 1986), enalapril cannot be considered a safe treatment for hypertension in pregnancy, owing to insufficient supportive information. Neonatal anuria was not observed in the present series, even though six patients received diuretics in association with captopril or enalapril. However, in the absence of laboratory data, we cannot dismiss the possibility of subclinical renal failure. Among the 15 pregnancies reviewed by Plouin & Tchobroutsky (1985) and the 21 pregnancies reported in this study that were exposed to captopril the ductus arteriosus remained patent in four infants and required surgical correction in two. Although preterm delivery and hypoxia could explain this abnormality (Cunningham *et al.* 1986), stimulation of a bradykinin-induced release of vasodilating prostaglandins might also play a role, since ACE is identical to kininase II. Close surveillance of renal function and ductus arteriosus closure is necessary in infants born to women exposed to ACE inhibitors during the last weeks of pregnancy.

References

Boutroy, M. J , Vert, P , Hurault De Ligny, B. & Miton, A. (1984) Captopril administration in pregnancy impairs fetal angiotensin converting enzyme activity and neonatal adaptation *Lancet* **ii**, 935-936

Broughton-Pipkin, F. & Wallace, C P. (1986) The effect of enalapril (MK 421), an angiotensin converting enzyme inhibitor, on the conscious pregnant ewe and her fetus *Br J Pharmacol* **87**, 533-542.

Cunningham, M D , Ellison, R. C , Zierler, S., Kanto, W. P., Miettinen, O S. & Nadas, A. S (1986) Perinatal risk assessment for patent ductus arteriosus in premature infants *Obstet Gynecol* **68**, 41-45

Duminy, P C. & Burger, P du T. (1981) Fetal abnormality associated with the use of captopril during pregnancy. *S Afr Med J* **56**, 805

Plouin, P F & Tchobroutsky, C (1985) Inhibition de l'enzyme de conversion de l'angiotensine au cours de la grossesse humaine *Presse Med* **14**, 2175-2178

Scanferla, F., Coli, U , Landini, S., Fracasso, A., Morachiello, P., Righetto, F., Genchi, R & Bazzato, G. (1986) Treatment of pregnancy-induced hypertension with ACE inhibitor enalapril *Fifth Congress of the International Society for the Study of Hypertension in Pregnancy,* Nottingham, Abstract 45

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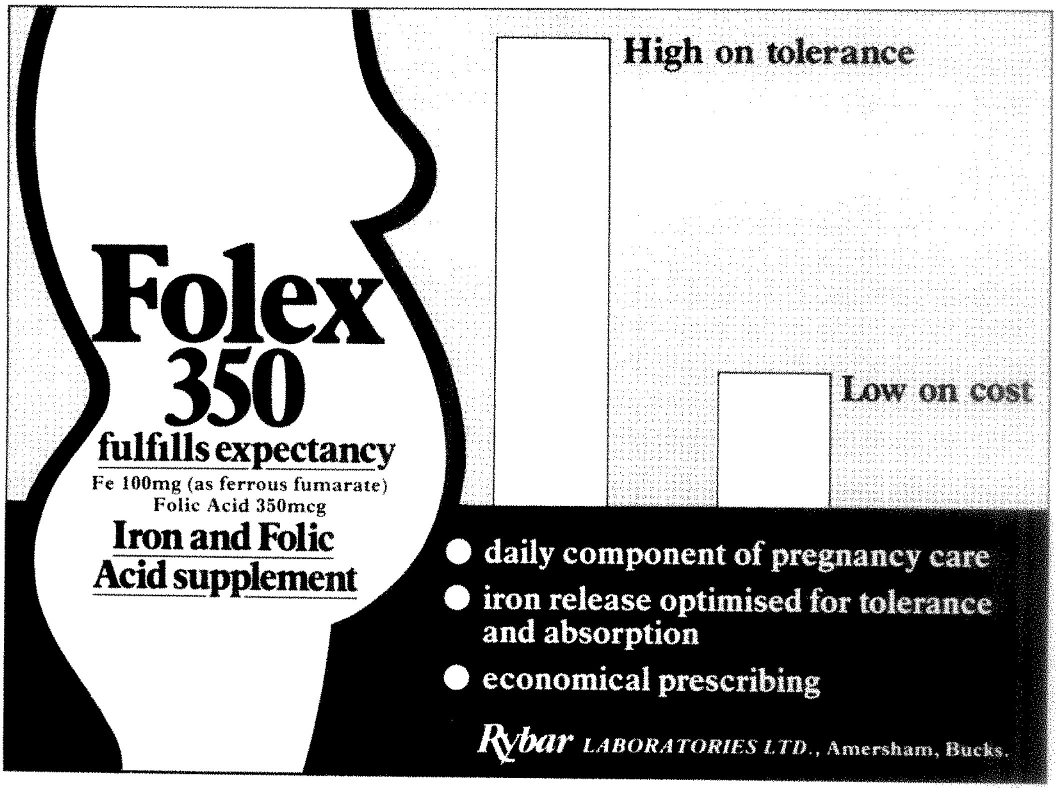

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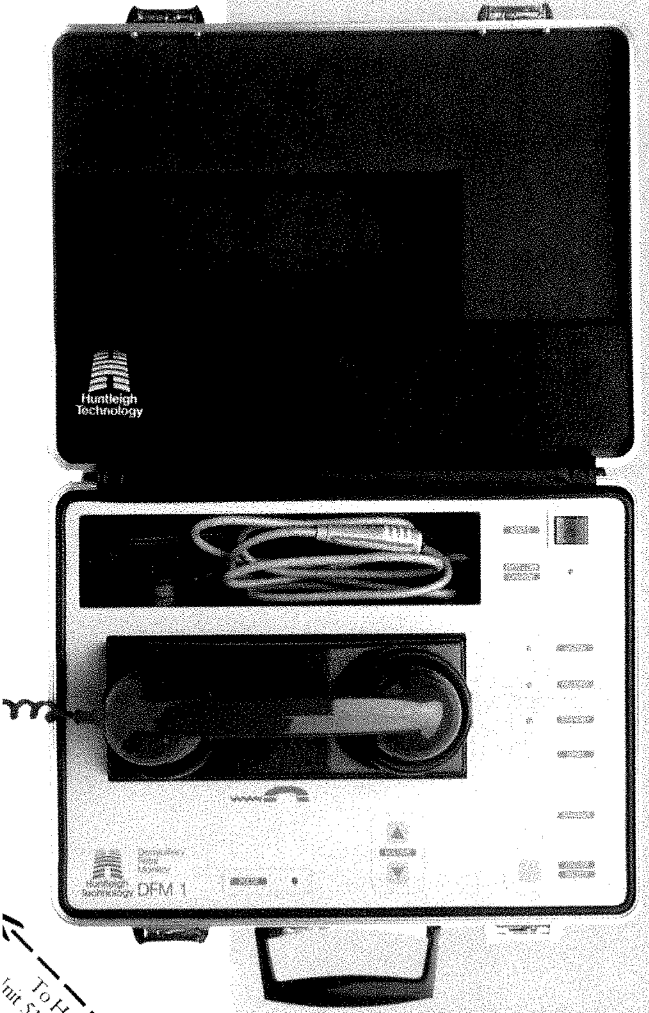
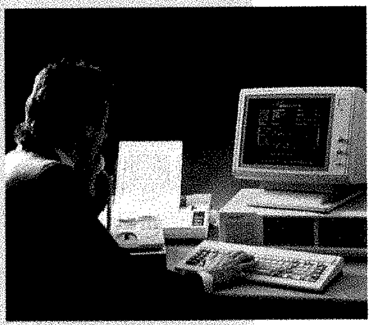
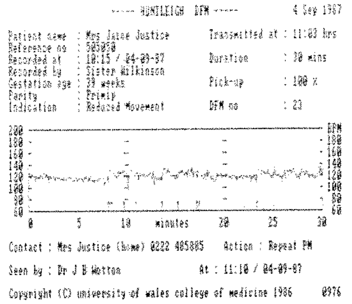




Huntleigh DFM allows antepartum monitoring to be carried out at the patients home or healthcentre...



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----- HUNTLEIGH  DFM -----          4 Sep 1987

Patient name    : Mrs Jane Justice        Transmitted at : 11:03 hrs
Reference no    : 505050
Recorded at     : 10:15 / 04-09-87        Duration       : 30 mins
Recorded by     : Sister Wilkinson
Gestation age   : 39 weeks                Pick-up        : 100 %
Parity          : Primip
Indication      : Reduced Movement        DFM no         : 23
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200
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Contact : Mrs Justice (home) 0222 485885    Action : Repeat FM

Seen by : Dr J B Wotton                At : 11:10 / 04-09-87

Copyright (C) university of wales college of medicine 1986      0976
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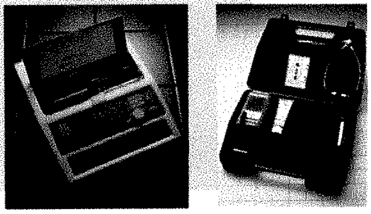
...and transmitted to hospital in 45 seconds for expert interpretation.

... AND MORE
FROM



Fetal Heart Detectors and blood flow dopplers for hospital and community.

HUNTLEIGH TECHNOLOGY

Huntleigh Technology plc Healthcare Division
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SEND

British Journal of Obstetrics and Gynaecology
April 1988, Vol. 95, pp. 423–426

CORRESPONDENCE

Natural killer cells in cervical intraepithelial neoplasia and human papillomavirus infection

Dear Sir,
In their study of natural killer (NK) cells in cervical intraepithelial neoplasia (CIN) and human papillomavirus (HPV) infection, Dr Tay and his colleagues [*Br J Obstet Gynaecol* (1987) **94,** 901–906] detected NK cells in the subepithelial stroma of most cases of HPV infection and CIN. In contrast, there were few intraepithelial NK cells in HPV infection and CIN. They suggest that this may be due to poor tumour antigenicity or a direct tumour effect or an effect of seminal plasma.

We believe the most likely explanation is that exposure of the cervix to seminal plasma inhibits NK activity in cervical epithelium. In general, human seminal plasma contains various agents which inhibit the normal immune response (Alexander & Anderson 1987), including the response of lymphocytes to a viral infection (Turner *et al.* 1987). More specifically, human seminal plasma has been shown to suppress NK cell activity (James & Szymaniec 1985; Tarter *et al.* 1986).

The inhibition of NK activity in cervical epithelium by repeated exposure to seminal plasma may promote both neoplasia and viral infections of the cervix. This is consistent with the documented epidemiological associations between cervical neoplasia and sexual behaviour (Kessler 1981).

M. J. Turner
J. O. White
W. P. Soutter
Institute of Obstetrics
and Gynaecology
Hammersmith Hospital
Du Cane Road
London W12 0HS

References

Alexander, N. J. & Anderson, D J. (1987) Immunology of semen. *Fertil Steril* **47**, 192-205.

James, K. & Szymaniec, S. (1985) Human seminal plasma is a potent inhibitor of natural killer cell activity *in vitro*. *J Reprod Immunol* **8**, 61-70.

Kessler, I. I. (1981) Etiological concepts in cervical carcinogenesis *Gynecol Oncol* **12,** S7-S24.

Tarter, T. H., Cunningham-Rundles, S. & Koide, S. S. (1986) Suppression of natural killer cell activity by human seminal plasma *in vitro:* identification of 19-OH-PGE as the suppressor factor. *J Immunol* **136,** 2862-2867.

Tay, S. K., Jenkins, D. & Singer, A. (1987) Natural killer cells in cervical intraepithelial neoplasia and human papillomavirus infection. *Br J Obstet Gynaecol* **94,** 901-906.

Turner, M. J., White, J O. & Soutter, W. P. (1987) Seminal plasma and AIDS. *Immunol Today* **8,** 258

Pregnancy and delivery by caesarean section in a patient with transposition of the great arteries and single ventricle. Case report

Dear Sir,
Bauman *et al.* [*Br J Obstet Gynaecol* (1987) **94,** 704–708] in their recent article on pregnancy and delivery in a patient with transposition of the great arteries (TGA), state that a later echo led to a new diagnosis of 'genuine' transposition with a single ventricle, as compared to a previous diagnosis of corrected TGA with a ventricular septal defect (VSD).

From the echocardiographic pictures which they present (Fig. 1, p. 705 and Fig. 2, p. 706) it is clear that their patient has a double inlet left ventricle with Levo TGA, probably with a subaortic chamber. The very large pulmonary artery suggests pulmonary hypertension, in the absence of pulmonary stenosis, probably even Eisenmenger syndrome. An additional ASD secundum is possible—at least as seen in these two figures.

Very often these patients benefit from pulmonary artery banding, as long as their pulmonary vascular resistance is lower than the systemic resistance.

Most probably, in this particular patient surgery cannot be suggested because of the high pulmonary vascular resistance.

The 'new' diagnosis, it seems to me, is even less accurate than the early diagnosis of corrected TGA.

Joram Glaser
Pediatric Cardiology Unit
Shaare Zedek Medical Center
Jerusalem
Israel

Author's reply

Dear Sir,

We have discussed Dr Glaser's letter with the cardiologists who were originally consulted in this case, since the points raised by Dr Glaser concern cardiological aspects.

The cardiologists agree that this form of single ventricle with transposition of the great arteries (TGA) can also be diagnosed as double inlet left ventricle with Levo TGA. They find no ASD. They also agree that pulmonary artery banding has to be considered, and that a decrease in arterial saturation, together with a very large pulmonary artery, suggests progressive pulmonary hypertension.

H. Baumann
Department of Obstetrics
University Hospital of Zurich
Frauenklinikstrasse 10
8091 Zurich
Switzerland

Additional comments from Dr Rigby

The patient described does appear to have the usual atrial arrangement (solitus), double inlet left ventricle, left-sided rudimentary right ventricle, ventriculo-arterial discordance with an anterior and left-sided aorta and pulmonary vascular disease. This patient is unlikely to benefit from banding of the pulmonary artery at this age as I am sure she does have irreversible pulmonary vascular disease. As it stands her prognosis is poor and the only treatment from which she would benefit would be heart and lung transplantation when this is clinically indicated. In view of this it is important that she should not have a thoracotomy with banding of the pulmonary artery as this would make heart and lung transplantation more hazardous and more difficult.

This case illustrates well the problems that arise from imprecise nomenclature.

M. L. Rigby
Consultant Paediatrician and Cardiologist
Brompton Hospital
Fulham Road
London
SW3 6HP

Pre-eclampsia in a woman with homozygous PIZZ alpha-1 antitrypsin deficiency. Case report

Dear Sir,

The report by Kennedy *et al.* [*Br J Obstet Gynaecol* (1987) **94**, 1103–1104] of pre-eclampsia and delayed postpartum haemorrhage in an α_1-antitrypsin (AAT)-deficient primigravida raises several interesting points. AAT and antithrombin III, the predominant plasma inhibitor of thrombin, belong to a 'superfamily' of protease inhibitors with similar molecular structures (Hunt & Dayhoff 1980). The similarity of the two inhibitors was confirmed by the occurrence of a spontaneous point mutation (358 Met→Arg) in the gene coding for AAT which resulted in loss of inhibition of elastase but a marked increase in inhibition of thrombin (Owen *et al.* 1983). The patient died of a bleeding disorder during an acute phase response, associated with a marked increase in concentration of the aberrant inhibitor (Lewis *et al.* 1978).

The most common coagulation disorder seen in AAT-deficient individuals is gastrointestinal bleeding from oesophageal varices and vitamin K deficiency secondary to severe liver disease (Sharp 1976). Otherwise, coagulation disorders are not typical findings in AAT deficiency (Fagerhol & Cox 1981), even though this protein may contribute as much as 25% of thrombin inhibition (Matheson & Travis 1976). The possibility that hypercoagulability might play a role in the pathogenesis of pulmonary emphysema in AAT deficiency has been suggested (Fagerhol & Cox 1981). This is analogous to the hypothesis of McKay *et al.* (1953) that the primary lesion in pre-eclampsia may be fibrin deposition in the basal and spiral arteries. As Kennedy *et al.* state, AAT may play a more significant role in thrombin inhibition during pregnancy (Teisner *et al.*

1982); levels of this protein are known to increase dramatically during pregnancy in women with the common Pi M phenotype (Ganrot & Bjerre 1967).

Although there have been no other published reports of pregnancies in women with severe AAT deficiency and either thrombosis or pre-eclampsia, five of 40 pregnancies in Pi MZ or SZ women carrying fetuses with severe deficiency were associated with pre-eclampsia (Sveger 1976; A. M. Johnson, unpublished observations). This percentage of affected pregnancies is not excessive; however, four of the five were second or third pregnancies, with no known history of hypertension or pre-eclampsia in previous pregnancies. This is in contrast to the usual predominance of these disorders in first pregnancies; indeed, it has been suggested that true pre-eclampsia occurs only in primigravidas (Ihle *et al.* 1987).

I have seen a male Pi Z infant with right testicular thrombosis and infarction at birth; a 26-year-old Pi Z woman who died postpartum with multiple thromboemboli, presumably secondary to amniotic fluid embolism; and three Pi S adult males with spontaneous deep vein thrombosis. It thus appears that AAT deficiency may be a contributing factor in thrombotic disease and in pre-eclampsia in affected individuals, although other factors are undoubtedly necessary to trigger the clotting diathesis.

A. M. Johnson
Foundation for Blood Research
Scarborough
Maine 04074
USA

References

Fagerhol, M. K. & Cox, D W. (1981) The Pi polymorphism: genetic, biochemical and clinical aspects of human α_1-antitrypsin. *Adv Hum Genet* **11,** 1-62.

Ganrot, P. O. & Bjerre, B. (1967) α_1-antitrypsin and α_2-macroglobulin concentration in serum during pregnancy. *Acta Obstet Gynecol Scand* **46,** 126-137.

Hunt, L. H. & Dayhoff, M. O. (1980) A surprising new protein superfamily containing ovalbumin, antithrombin III, and α_1-proteinase inhibitor. *Biochem Biophys Res Commun* **95,** 864-871.

Ihle, B. U., Long, P & Oats, J. (1987) Early onset pre-eclampsia: recognition of underlying renal disease *Br Med J* **294,** 79-81.

Lewis, J. H., Iammarino, R. M., Spero, J. A. & Hasiba, U. (1978) Antithrombin Pittsburgh: an alpha 1-antitrypsin variant causing hemorrhagic disease. *Blood* **51,** 129-137.

McKay, D G., Merrill, S J , Weiner, A E., Hertig, A. T. & Reid, D. E. (1953) The pathologic anatomy of eclampsia, bilateral renal cortical necrosis, pituitary necrosis, and other acute fatal complications of pregnancy, and its possible relationship to the generalized Shwartzman phenomenon. *Am J Obstet Gynecol* **66,** 507-539

Matheson, N. R. & Travis, J. (1976) Inactivation of human thrombin in the presence of human α_1-proteinase inhibitor. *Biochem J* **159,** 495-502.

Owen, M. C., Brennan, S O., Lewis, J. H. & Carrell, R W. (1983) Mutation of antitrypsin to antithrombin. *N Engl J Med* **309,** 694-698.

Sharp, H. L. (1976) The current status of α-1-antitrypsin, a protease inhibitor, in gastrointestinal disease. *Gastronenterology* **70,** 611-620

Sveger, T (1976) Alpha$_1$-antitrypsin deficiency in early childhood. Thesis, Malmö General Hospital, University of Lund, Malmo, Sweden.

Teisner, B., Davey, M. W. & Grudzinskas, J. G. (1982) Circulating antithrombins in pregnancy. *Br J Obstet Gynaecol* **89,** 62-64.

Is treatment needed for mild impairment of glucose tolerance in pregnancy? A randomized controlled trial

Dear Sir,

We read with interest the article by Li *et al.* [*Br J Obstet Gynaecol* (1987) **94,** 851–854] and we do not agree either with the proposed treatment of gestational diabetes or with the authors' conclusions.

The achievement of normoglycaemia is the key to the management of diabetes during pregnancy (Jovanovic *et al.* 1980), and we are given no information about the tightness of metabolic control in either group.

Additionally, treatment seems not to consider insulin therapy whereas it is included in the recommendations of the Second International Workshop on Gestational Diabetes (1985). In our own experience, 70 of 100 gestational diabetics needed insulin therapy to achieve or maintain normoglycaemia, which coincides with other published data (Berne *et al.* 1985).

If we consider outcome, control and treatment groups did not differ, but the high rate of macrosomia was far from optimal, and although no hypoglycaemia was recorded, it could be due to the use of a lower than usual diagnostic criterion (Cornblath & Reisner 1965). The prevalence of other classic complications of diabetic pregnancy (polyhydramnios, pre-eclampsia, neonatal hypocalcaemia, hyperbilirubinaemia or polycythaemia) (Pedersen 1977) are not mentioned in the article whereas they are important issues to assess the outcome.

We agree with the authors that treatment did not make a difference in their study. Nevertheless, in our opinion the suboptimal treatment administered made control and treated groups too much alike.

R. Corcoy
M. Codina
A. de Leiva
Servicio de Endocrinologia y Nutrición
M. J. Cerqueira
L. Cabero
Servicio de Ginecologia y Obstetricia
Hospital de la Sta Creu i Sant Pau
Universitat Autònoma de Barcelona
Avda Sant Antoni Ma Claret, 167
Barcelona 08025
Spain

References

Berne, C., Wibell, L. & Lindmark, G. (1985) Ten-year experience of insulin treatment in gestational diabetes *Acta Paediatr Scand* **(Suppl.) 320,** 85-93.

Cornblath, M. & Reisner, S. H. (1965) Blood glucose in the neonate and its clinical significance. *N Engl J Med* **273,** 378-381.

Jovanovic, L., Peterson, C. M., Saxena, B. B , Dawood, M. Y & Saudek, C. D (1980) Feasibility of maintaining normal glucose profiles in insulin-dependent pregnant diabetic women. *Am J Med* **68,** 105-112.

Pedersen, J. (1977) *The Pregnant Diabetic and Her Newborn.* Munksgaard, Copenhagen, pp. 89-193.

Second International Workshop-Conference on Gestational Diabetes Mellitus (1985) Summary and Recommendations. *Diabetes* **34 (Suppl. 2),** 123-126.

Author's reply

Dear Sir,

In the description of the methods of our study it was stated that patients diagnosed as overt gestational diabetes mellitus after the 75 g OGTT (fasting ≥8·0 mmol/l or 2 h ≥11·0 mmol/l) were excluded from randomization for ethical reasons. In line with Dr Corcoy's observation, many of these patients required insulin treatment for optimal metabolic control. Our study aimed to address the problems of patients with mild gestational glucose intolerance—is treatment required or not? The control group was not dieted nor were their glucose profiles checked during pregnancy because they were 'double-blind'. Those who were treated had their glucose profiles checked periodically achieving a target pre-prandial level of <6·0 mmol/l and postprandial level <7·0 mmol/l. At the time of delivery, there was no significant difference in the mean glycosylated haemoglobin level between the no-treatment and treatment group, 7·3% and 8·1% respectively (normal range up to 8% in our laboratory). It can be seen that the HbAl was within the normal range in most patients. The occurrence of complications such as polyhydramnios, pregnancy-induced hypertension and hyperbilirubinaemia is rather uncommon and did not differ between the two groups. Hence, the conclusion that treatment seems to make no difference in these patients is probably because they started off with either normal glucose tolerance or at the most very mild impaired glucose tolerance; not in our opinion due to suboptimal treatment.

Dominic Li
Lecturer
Department of Obstetrics and Gynaecology
University of Hong Kong
Queen Mary Hospital
Hong Kong

Reference

Li, D F. H., Wong, V. C. W., O'Hoy, K. M. K. Y., Yeung, C. Y. & Ma, H. K. (1987) Is treatment needed for mild impairment of glucose tolerance in pregnancy? A randomized controlled trial. *Br J Obstet Gynaecol* **94,** 851-854

British Journal of Obstetrics and Gynaecology
April 1988, Vol. 95, pp. 427–432

BOOK REVIEWS

Spontaneous and Recurrent Abortion edited by Michael J. Bennett & Keith Edmonds. Blackwell Scientific Publications, Oxford, 1987, 248 pages with figures and tables, £29.50

To a couple looking forward to a child, miscarriage, even very early in pregnancy, seems a unique disaster, and they have high expectations of diagnosis and prognosis. To the professional, the complexity of implantation and embryogenesis presents so many cliff-hanging moves that reaching the third trimester with a healthy child seems a triumph of nature. This book collects together many facts and figures about early pregnancy loss which helps to fill the gap between these spectral ends.

The topics covered are concerned with spontaneous and recurrent abortion and include embryological, epidemiological, chromosomal, immunological, anatomical, exogenous and psychological factors. Until recently, spontaneous abortions were so intermingled with fresh, induced ones, that the relative importance of prior embryonic death was not always appreciated. The value of careful pathological examination of conceptus tissue is well discussed. Epidemiological factors are difficult to unravel, and the many pitfalls of over-naive interpretation are fully ventilated. The new, rapidly developing field of the study of immunopathological factors provides background information essential for the understanding of new interventions. Congenital anomalies are included. While there is not much new in the description, classification and clinical correlates of anatomical abnormalities of the uterus, there is a very informative section on operative techniques and their outcome.

A chapter on DES exposure sets out a coherent account of the reproductive aftermath in this generation of girls. The current uncertain status of infection as a cause of abortion is reviewed. One of the most readable chapters gives an autobiographical account of the treatment of cervical incompetence. It makes fascinating reading both to those who were aware of this developing story and perhaps more importantly to the young clinician of today to whom the brevity of the history of this treatment may come as a revelation. The enigma of recurrent abortion and the relative importance of chance and causal factors is an area of current concern and the present views on causation are reviewed. The minefield of current therapeutic endeavour is skirted. Assessment of psychological factors and the relative importance of effect rather than cause complete these chapters.

The role of vascular and biochemical factors is relatively neglected and the emphasis of the book is clearly morphological and anatomical. The authors have not knitted the chapter contributions into a coherent style—they range from mundane through sparkling to leaden. The references are comprehensive. This is a book for the clinician with a concern for the study of abortion. Teaching, clinical observation and informed discussion with the distressed couple will all benefit from its study. It has been a neglected area in the past and the authors are to be congratulated on making the effort to get this collection together.

Sheila Duncan

Baillière's Clinical Obstetrics and Gynaecology Vol. 1 No. 1 Fetal Monitoring edited by Martin Whittle. Baillière Tindall, London, Philadelphia, 1987, 222 pages with figures and tables, UK & Eire £15.00, USA & Canada $25.00, all other areas £18.00

In this volume Martin Whittle has succeeded admirably in drawing together a series of succinct reviews of the important aspects of fetal monitoring. The text is suitable both for the resident studying for higher qualifications and for the specialist wishing to update his knowledge. There are 11 chapters, discussing both antenatal and intrapartum fetal monitoring. The antenatal period is covered by reviews of biochemical, cardiotocographic and ultrasonic monitoring (including the biophysical profile and blood velocity waveform measurement). Long-established techniques for monitoring the intrapartum period such as cardiotocography and acid base balance are critically assessed, as are methods such as analysis of the ECG waveform and systolic time interval which have been around a long time without ever having proved their clinical value. The authors are international, with six from Scotland, five from Canada, three from England, three from the USA and one from Singapore, and all write with the distinction that comes from mastery of their field of expertise. The editor has generally coped well with blending a variety of writing styles into a readable and consistent whole, although Frank Manning's tendency to the North American habit of lapsing into long jargon-laden phrases with multiple subclauses has not been entirely curbed. There are also some jarring comments; for example Peter Boylan in an otherwise excellent chapter on cardiotocography strongly advises against the placement of an intrauterine pressure catheter despite the excellent case made out for the technique by Donald Gibb and Sabaratnam Arulkumaran in their chapter on the assessment and management of uterine contractions. Presentation of the volume is excellent with few printing errors. Altogether, highly recommended.

Philip J. Steer

Magnetic Resonance of the Reproductive System edited by Shirley McCarthy & Florence Haseltine. Slack Incorporated, Thorofare, New Jersey, 1987, 230 pages with figures and tables, £45.60

In May 1986, the Center for Population Board of the National Institute of Child Health and Human Development sponsored a workshop on magnetic resonance imaging and spectroscopy and this book is essentially the report of that meeting. There are 16 chapters and 17 principal contributors. It must be stated at the outset that only four of these chapters have any real clinical relevance at the present time and the major emphasis of the book is on magnetic resonance spectroscopy and not on imaging, and indeed, the quality of images on human subjects reported in this book is generally poor and limited in range and number. Nevertheless, the chapters on basic concepts, biological applications of magnetic resonance spectroscopy and uterine bioenergetics using ^{31}P were particularly interesting. The section on biohazards raises issues that are particularly important in the future of the technique in pregnancy and so far the work appears to offer reassurance that the procedure is safe, at least in the animal models reported

The editors have done a valuable job in putting this report together. One suspects that the value of the workshop to the people involved in this field was rather greater than that of the report which it has generated is to practising obstetricians and gynaecologists.

The book is one of speculation because there was insufficient actual information available at the time to justify a full volume on magnetic resonance and the reproductive tract. It is therefore a book for those clinicians and scientists with a particular interest in this field and not a volume that will be of value to the uninitiated.

E. M. Symonds

Neonatal Medicine edited by Leo Stern & Paul Vert. Masson Publishing USA, Inc., New York, 1987, 1215 pages with figures and tables, £81.00

Until recently, most major textbooks of neonatal medicine were of all-American parentage, but in the last year or two the balance has been redressed. *Neonatal Medicine* is a truly international compendium of formidable proportions; nine parts, 47 chapters and 80 authors from Europe, North America and occasionally elsewhere. The book is the English version (with some updating) of the French language *Medecine Neonatale,* and the authors contributed their chapters in both languages, rather than this being a translation. The emphasis of the book is towards basic sciences and a perinatal approach despite the title, and it is not an 'intensive care cook-book'!

The most impressive feature of this book is its comprehensiveness. Strong chapters include those on neonatal neurology and developmental anatomy, inborn errors of metabolism and neonatal infection The latter is appended with a page on AIDS. For a book on neonatal 'medicine', surgery is well covered, although with a developmental rather than an operative bias.

Although the theoretical basis of all aspects of neonatal medicine is there, practical advice is more difficult to find. 'Assisted ventilation in the newborn' occupies 10 of the book's 1200 pages, although other snippets of practical aspects are to be found amongst related chapters. On the other hand 49 pages are devoted to neonatal tumours. The use of diagnostic ultrasound in neonatal neurology and cardiology is hardly mentioned, giving the book a slightly dated feel.

Neonatal Medicine is more a book of reference than a textbook or guidebook for the learner, and as such will find a deserved place in larger libraries, but probably not on the resident's bookshelf.

Richard Cooke

Drug Therapy in Obstetrics and Gynecology. Second edition edited by William F. Rayburn & Frederick P. Zuzpan. Appleton-Century-Crofts/Norwalk, Connecticut, 1986, 512 pages with figures and tables, $65.55, £50.85

The editors, an obstetric clinical pharmacologist and a gynaecologist, both well-known figures, say in their preface that this second edition was written to provide updated information about drugs used primarily by women. There are 37 contributors, all American, 24 of whom are drawn from the considerable body of expertise in Ohio, but the editors themselves contribute a substantial number of the chapters in the obstetric half of the book.

The first chapter, on principles of perinatal pharmacology, I found a little confusing: 'a drug crosses cell membranes selectively by many transport mechanisms'—hardly a true generalization. The placental membrane is stated to have a thickness of 2 mcg *(sic)* at term *between the placental capillaries*. Mitochondria are said to be the main intracellular sites for drug metabolism. Protein binding is stated to be lower in fetus than mother (untrue for albumin binding at term) yet local anaesthetics to be at higher concentration at equilibrium in fetus than in mother, whereas, being glycoprotein bound, the reverse is true.

After this rather misleading start, the next chapter on drug effects on the fetus was orderly and more authoritative and, in common with the rest of the book, contains some useful and comprehensive tables.

Several chapters cover management of various disease states in pregnancy, with no important omissions, though it was odd to see in a book published in 1986 a list of complications that drug addicts may suffer, with no mention of AIDS. Also, no real recommendations were made about the problem of managing women with prosthetic heart valves in pregnancy.

A problem in writing any book of this nature is that the descriptions of the different medical conditions and of the pharmacology of the individual drugs tend to displace any discussion of their specific relationships to obstetrics and gynaecology. This applies particularly to the chapter on cardiac drugs. Such an approach may produce exactly what the obstetrician wants to read but would appear to condone ad lib prescribing in pregnancy. The untutored mind is often more worried about drug transmission in breast milk than across the placenta—a fallacious concern that this book does not always dispel.

Nevertheless, chapter headings are well chosen and presented in orderly sequence. Following general medical considerations come chapters on maternal immunization, fetal lung maturation, inhibition of premature labour, uterine stimulation, management of pain, care of the newborn, and lactation. It is stated in several places that the mechanisms of action of various drugs are unknown which may be true from some points of view, but overlooks the fact that a lot *is* known about the mechanisms, though clearly not to the authors! It is rather odd to see acupuncture classed as a psychological technique of analgesia.

The gynaecological section of the book is also well planned, with authoritative chapters relating to the use of sex hormones, induction of ovulation, over-the-counter drugs, therapy of infections, urological disorders, endometriosis etc, cancer chemotherapy and parenteral nutrition. Again much of the information is general but certainly appropriately selected for a gynaecological readership. Numerous steroid formulae feature in figures in a number of chapters, with mention in the text of the effect of substitutions on different parts of the molecule, yet nowhere is the numbering of the different positions of the steroid nucleus shown—surely necessary for at least *some* clinicians.

The text contains some spelling mistakes and clumsy English, making rather irritating reading in places. To cite a few examples: 'aminocentesis'; amine groups labelled 'amide'; 'two times' (instead of 'twice'); 'menopausal syndrome' instead of 'menopause'; 'Administration must be given intravenously or subcutaneously'; 'The occurrence of ischaemic heart disease may be more common . . .'; 'grams' written 'gms' instead of 'g'; and perhaps best of all. 'Neither the ideal agent(s) nor the ideal method of administration has not been identified at this time'

In the preface, the editors state that the text is aimed at 'practicing *(sic)* physicians, house officers and students in all disciplines'. My own view is that students need a more general approach to therapeutics, and that though clinicians would undoubtedly find some of the tables useful, they might have difficulty in knowing how much reliance to place on the text. It is a pity that a book that has been well planned to cover exactly the right subject matter is so uncertain in its execution.

F. Reynolds

Medical and Experimental Mammalian Genetics: A Perspective. March of Dimes Birth Defects Foundation Original Article Series Volume 23 Number 3 edited by V. A. McKusick, T. H. Roderick, J. Mori & N. W. Paul. Alan R. Liss, Inc., New York, 1987, 358 pages with figures and tables, no price given

This book contains 14 papers collected to celebrate the first 27 years of the 'Bar Harbor Course' in medical and experimental mammalian genetics. The Bar Harbor Course is a great course. Held at the Jackson Laboratory on Mount Desert Island, a national park on the coast of Maine, the 2-week course not only provides an update for busy clinicians and researchers, but also covers exciting work-in-progress by the lecturers, who are at the forefront of their fields. The statement in the book that the Bar Harbor Course 'is a tradition like the British Crown' may be out by a few orders of magnitude, but there is nothing else like it for the clinical and mammalian geneticist.

To appreciate this book you have to be the sort of person who is excited by the latest discoveries and concepts in molecular biology and genetics. For example, if the statements that 'the entire human mitochondrial DNA genetic code can be read using only 22 tRNAs, rather than the traditional 32' and that 'this is accomplished by inclusion of an unmodified U in the tRNA wobble position that can recognise all four members of a codon family' do not send a shiver up your spine, then this book is not for you. Otherwise read on.

All the reviews are outstanding so it is invidious to have to pick out a few. McKusick and Roderick give a fascinating historical review of 25 years in medical genetics and experimental mammalian genetics with particular reference to the gene map of mouse and man. Orlando Miller gives an outstanding review of the structure and organization of mammalian chromosomes. There are excellent reviews on the molecular techniques for gene mapping and diagnosis of genetic disorders, and of the molecular nature of mutations. For those interested in unusual genetic mechanisms, there are reviews of retroviral DNA, eukaryotic transposable elements, and mitochondrial genes and disorders. Sam Boyer and Edward Birkenmeier provide excellent reviews of current concepts in molecular and human evolution. Finally, given the venue of the course at the Jackson Laboratory there is an excellent review of mouse models of genetic diseases.

If you can't get to Bar Harbor, this volume is the next best thing. It fully reflects the excitement of the course.

R. M. Winter

Recent Advances in Obstetrics and Gynaecology 15 edited by John Bonnar. Churchill Livingstone, Edinburgh, 1987, 282 pages with figures and tables, £20.00

It is a pleasure to read this most recent *Advances* and the quality and standards of this, the 15th edition, are as good as ever. However, I would like to make a few brief comments and criticisms. In the first chapter on hypertension it is implied that patients with latent essential hypertension are not recognized early enough because they are not seen until the normal mid-trimester fall in blood pressure has taken place. It is my experience that most pregnant women now consult a doctor with a wanted pregnancy sometime between 6 and 8 weeks of amenorrhoea. I would have liked some data on the epidemiology of hypertension in pregnancy and also the effects of cigarette smoking in this disease. In the chapter on tropical diseases it is fascinating to learn that urinary oestriol estimations in leprosy are often low. I would prefer in this chapter for the spelling of fetus to be without the *o*! The table on the cost of antibiotics ought to be mandatory in all future medical publications; I presume that the prices mentioned are for the UK and are not the same as those charged overseas. The chapter 'Dilemmas in the treatment of preterm labour and deliveries', confirms my prejudices that the use of beta-mimetic agents does not improve fetal salvage and needs to be urgently put to a randomized trial similar to that taking place in Canada. The author also expresses considerable doubt about the use of steroids in preterm labour; similarly, the need for more surgical intervention in breech deliveries is not proven or advocated. This is a chapter to be read by all aspiring MRCOG candidates, as is that on fetal *(sic)* surveillance. Stanton's chapter on urinary incontinence should be usefully read by all of us whose first or second vaginal repair has failed to effect a cure.

The chapter on 'Sexually transmitted disease' contains the first account of the acquired immune deficiency syndrome (AIDS) that I have come across in a gynaecological textbook. It helps to be jogged into the realization that this disease is coming our way. It is important to be informed that *Chlamydia* is now the commonest cause of non-specific genital infection and that clinical signs of genital infection such as candidiasis and trichomoniasis are totally unreliable (p. 127). On p. 135 nonoxymol is spelt incorrectly with an *m* but it is the only typographical error I can find in the book. The section on advances in the treatment of germ cells of the ovary is a wise and inclusive update of these rarer gynaecological tumours as is the piece on the treatment of pre-invasive and invasive carcinomas of the vulva. It is notable that this author (C. Paul Morrow) is more emphatic than previous authors that these diseases are probably autoimmune phenomena. The chapter on 'Steroid hormone receptors in gynaecological causes' has brought me up to date on a difficult subject that I am sure is normally neglected by generalist gynaecologists. Family planning and sterilization are usefully covered with further emphatic emphasis on the known failure rate in all methods of sterilization.

Finally the chapter on polycystic ovary syndrome is timely and comprehensive with an excellent collection of references. Similarly the ultimate chapter on gonadotrophin-releasing hormone is thorough and offers practical help to the clinician.

J. McGarry

Fetal and Neonatal Pathology edited by Jean W. Keeling. Springer-Verlag, London, Heidelberg, 1987, 587 pages with figures and tables, £99.00

New medical textbooks are commonplace; those that fill a genuine gap in the market are particularly welcome. This new volume presently stands alone as a comprehensive and detailed account of the pathology of the fetus and neonate, following in the tradition of Edith Potter's textbook. Jean Keeling has assembled a team of authors from the UK and Europe, many of whom are wholly committed to the perinatal field, and allowed them to contribute in their special area of interest. The layout is not dissimilar to 'Potter' and there are two main sections with 15 chapters on general topics and 13 chapters on system pathology. The latter are truly comprehensive and include skin, eyes, and ears. These are all sound contributions to which the inexperienced pathologist can turn for assistance with confidence. Even the more experienced need guidance on rare conditions and the authoritative section on the osteochondro-dysplasias, for example, is a model in this respect.

The general ('problem-oriented') section on the other hand will interest those in other disciplines as well as histopathologists. The inclusion of sections on genetic aspects, epidemiology and immunology contributed by specialists in these fields helps to put perinatal pathology in perspective. Four chapters—'The perinatal necropsy', 'Spontaneous abortion and the pathology of early pregnancy', 'Examination of the fetus following prenatal suspicion of congenital abnormality' and 'Macerated stillbirth'—provide a useful synopsis of current 'good practice' in fetal and neonatal pathology. Other areas covered in this section are 'Placenta and umbilical cord', 'Genetic metabolic disease', 'Prematurity', 'Intrapartum asphyxia and birth trauma', 'Fetal hydrops', 'Congenital tumours', 'Infection', and 'Iatrogenic disease'.

Repetition and overlap are problems inherent in this format of 'problem-oriented' and systematic sections. There is a certain irritation in searching through several chapters in order to harvest all the available information on a specific topic such as toxoplasmosis, triploidy or twin transfusion syndrome, particularly where the cross-referencing in the text is incomplete. However, this has to be balanced against the benefit to the trainee of reviewing a general area such as spontaneous abortion or fetal hydrops in a single chapter. The most disappointing feature of the book is the variable quality of the illustrations and hopefully this can be improved for future editions.

This book is intended primarily for pathologists. Indeed it should be an essential requirement wherever perinatal pathology is practiced. However, it deserves a wider readership and is highly commended to trainees in obstetrics and neonatology.

A. A. M. Gibson

Reproductive Surgery edited by Alan De Cherney & Mary Lake Polan. Year Book Medical Publishers, Chicago, London, 1986, 335 pages with figures and tables, £48.00

Multi-author American medical books seem to proliferate like SALT II treaties. This 300+-page volume on reproductive surgery is produced by a wealth of experts whose ability to correct the ravishes of promiscuous sex is comprehensively covered. As with most American tomes, I find the chapters extremely long and verbose. There is much non-scientific speculation and too little reliance on the experimental method for delineating whether or not a treatment is effective. Despite the waspish beginning to this review, the book should not be damned entirely. It contains useful thoughts on laser surgery, microsurgery and prostheses, and for any gynaecologist who wishes to improve his expertise in these fields it would be £45 well spent. However, it is probably better bought by a library rather than an individual.

J. McGarry

Books received some of which may be reviewed at a later date

Essential Obstetrics and Gynaecology by E. Malcolm Symonds. Churchill Livingstone, Edinburgh, 266 pages illustrated, £14.95

Premenstrual Syndrome by P. M. Shaughn O'Brien. Blackwell Scientific Publications, Oxford, 1987, 222 pages with figures and tables, £24.50

Neonatal Cardiopulmonary Distress edited by George C. Emmanouilides & Barry G. Baylen. Year Book Medical Publishers, Inc., Chicago, 352 pages with figures and tables, £37.50

Women's Problems in General Practice Second edition edited by Ann McPherson. Oxford Medical Publications, Oxford, 1988, 473 pages with figures and tables, £17.50

Foundations of Obstetric Anaesthesia edited by Barbara M. Morgan. Farrand Press, London, 1987, 309 pages with figures and tables, £19 80

MRCOG Part 1 edited by Tim Chard & Richard Lilford. Springer-Verlag, London, 1987, 122 pages, £6.95

Proceedings and Symposia

Endometriosis (Contributions to Gynecology and Obstetrics. Volume 16. International Symposium on Endometriosis, Clemont Ferrand, 1986) edited by M. A. Bruhat & M. Canis. Karger, Basel, 1987, 394 pages with figures and tables, £104, Sw.Fr.230

Osteoporosis 1987 Volumes 1 and 2 (Proceedings of the International Symposium on Osteoporosis, Denmark, 1987) edited by C. Christiansen, J. S Johansen & B. J. Riis. Glostrup Hospital, University of Copenhagen. Vol. 1, pp. 5–637; Vol. 2, pp. 641–1285. Both with figures and tables, D.Kr. 1200

Reproductive and Perinatal Medicine VIII. Doppler Ultrasound Measurement of Maternal-Fetal Hemodynamics (Proceedings of a National Institute of Child Health and Human Development Research Planning Workshop held in Washington D.C. 1986) edited by D. Maulik & D. McNellis. Perinatology Press, Ithaca, New York, 1987, 306 pages with figures and tables, $60.00

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Altman D. G., Gore, S. M., Gardner, M. J. & Pocock, S. J. (1983) Statistical guidelines for contributors to medical journals. *Br Med J* **286**, 1489–1493.

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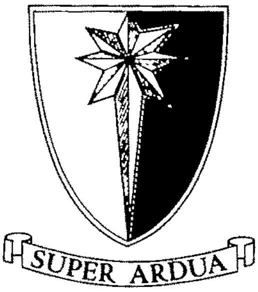
Edited by Frank E. Hytten



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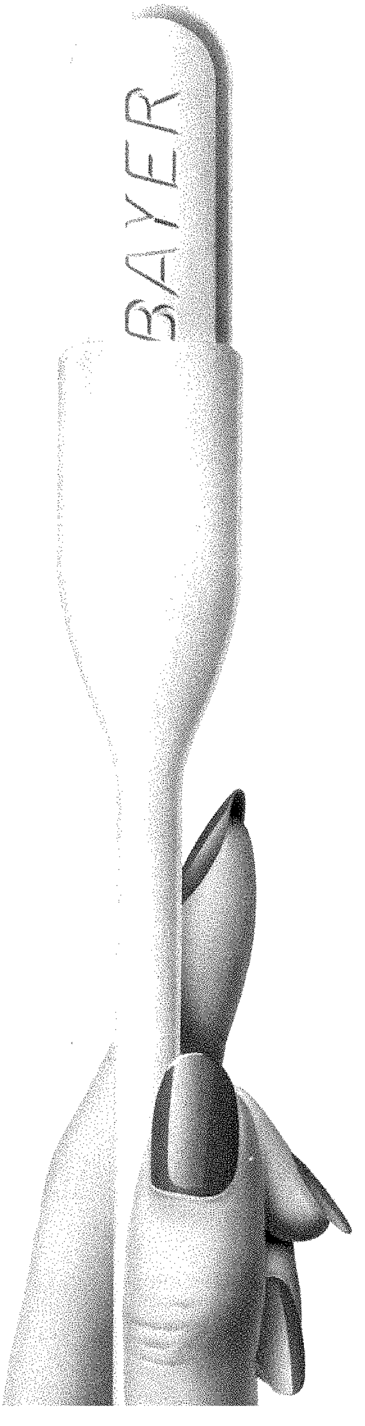

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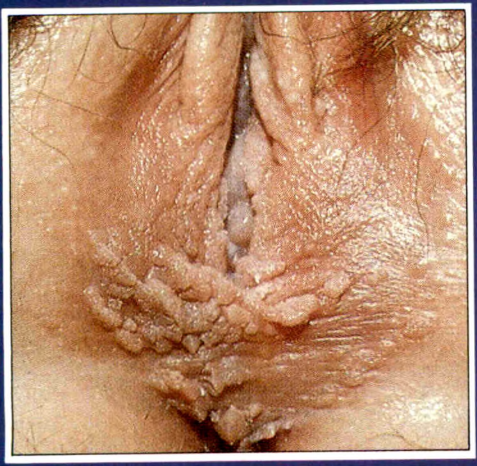

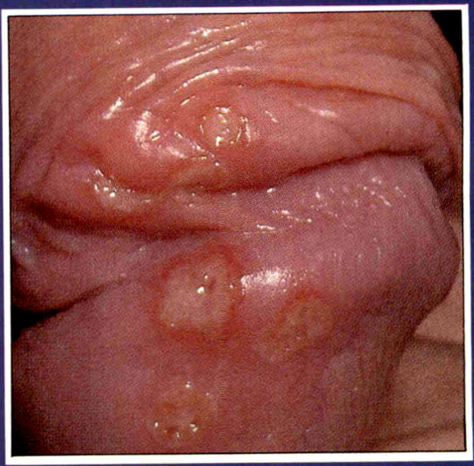

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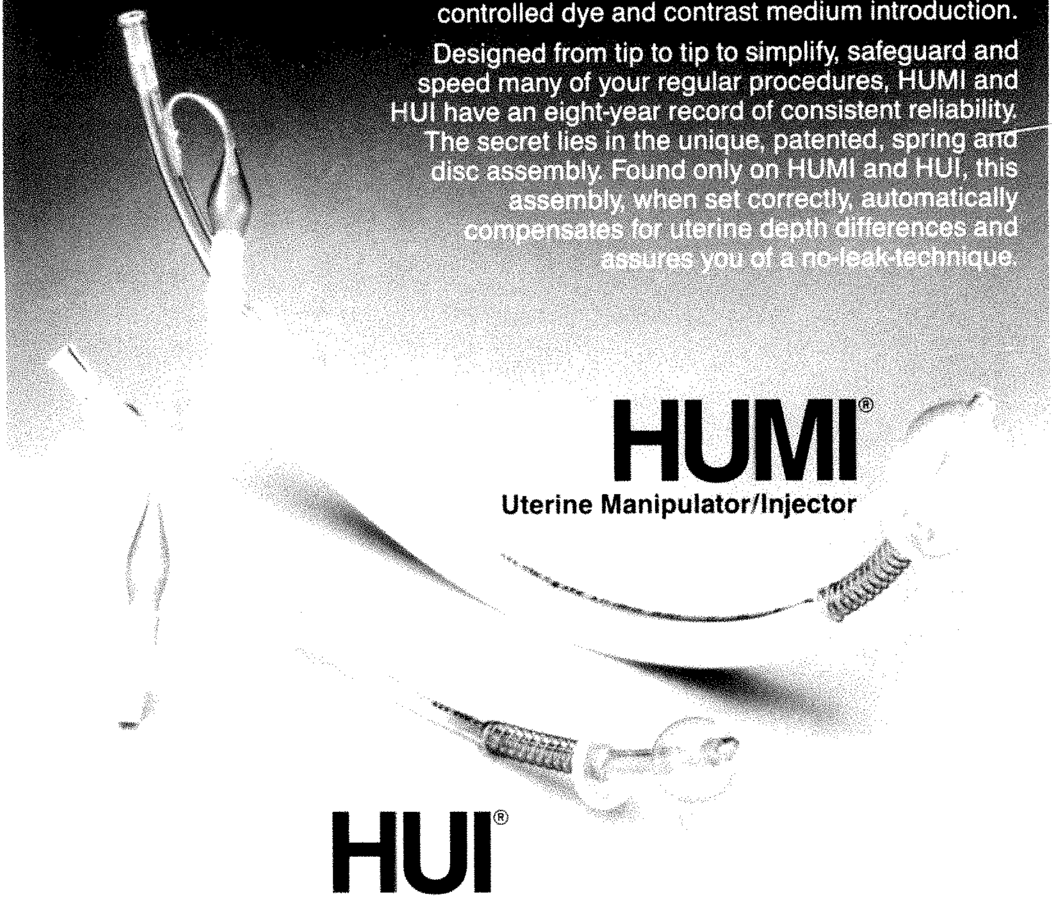

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References
1 Traub A (in press) 2 Yen S S C et al [illegible] 19 435 3 Polson D W et al Clinical Endocrinology (19[illegible]) 26 205 4 K[illegible] M.M. et al (1982) Fertil Steril 37 520 5 Jones [illegible] 1985 Steril 43 696

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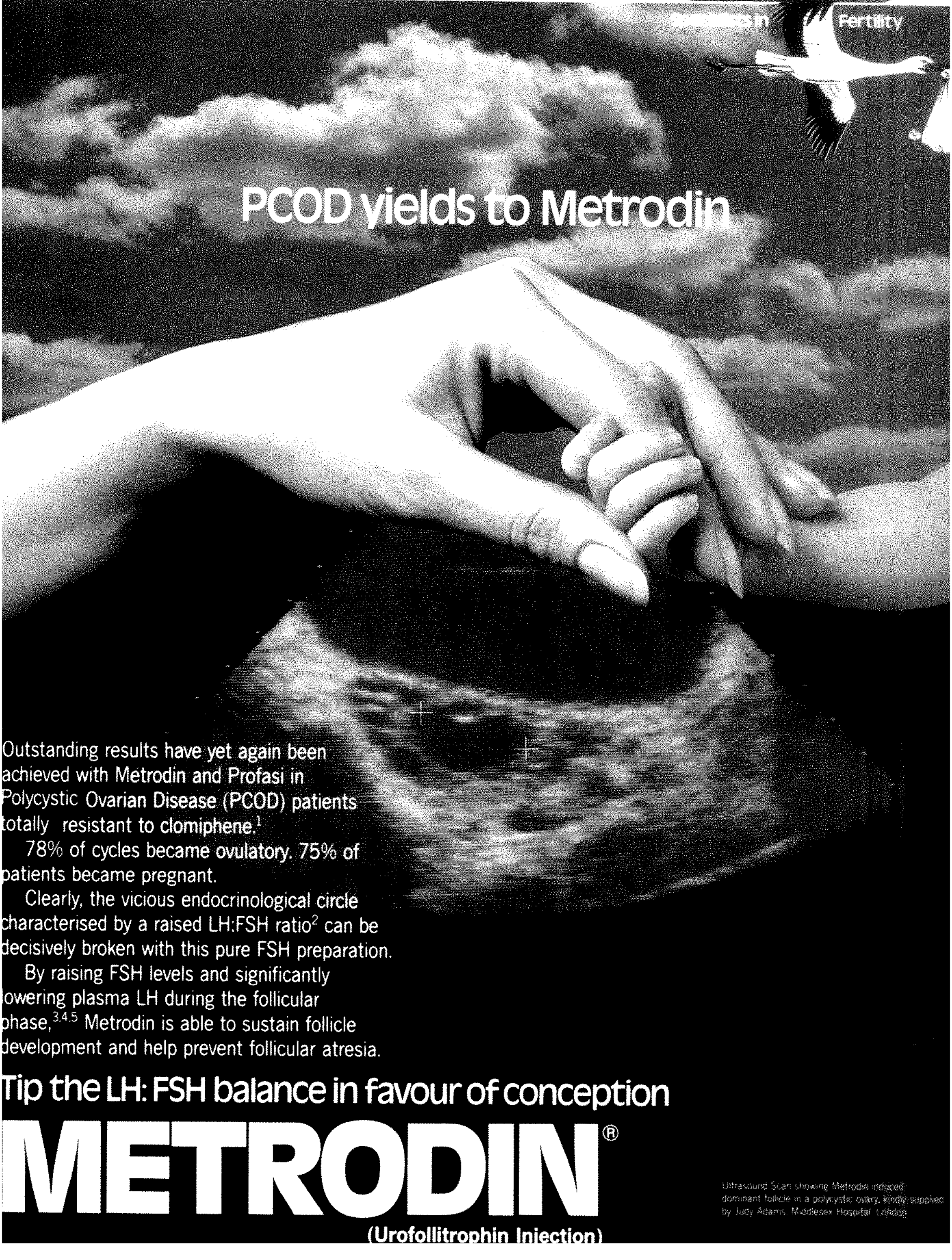

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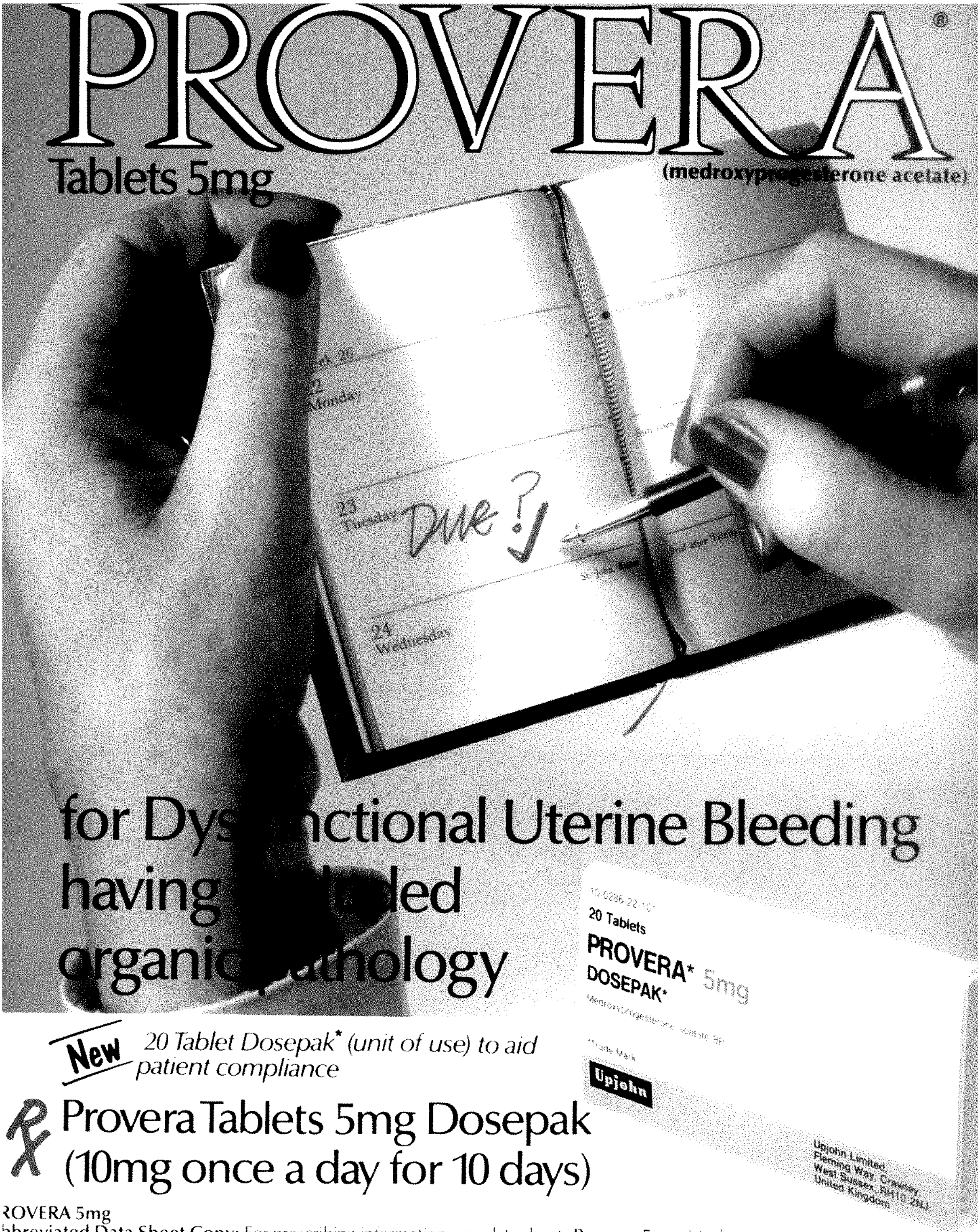
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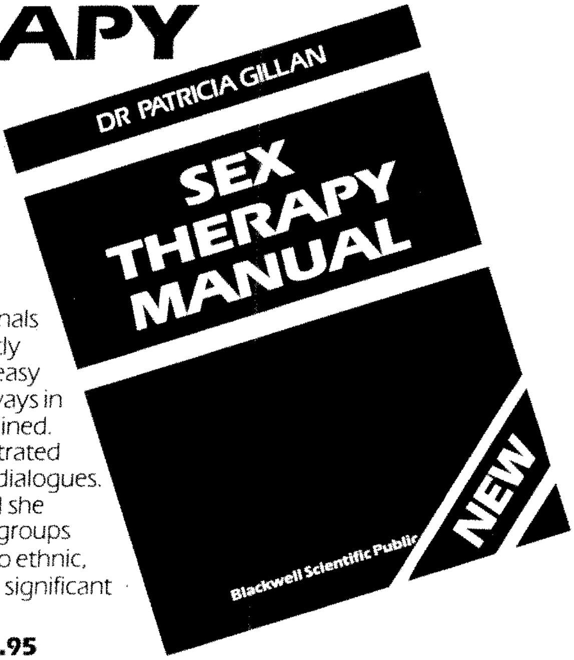

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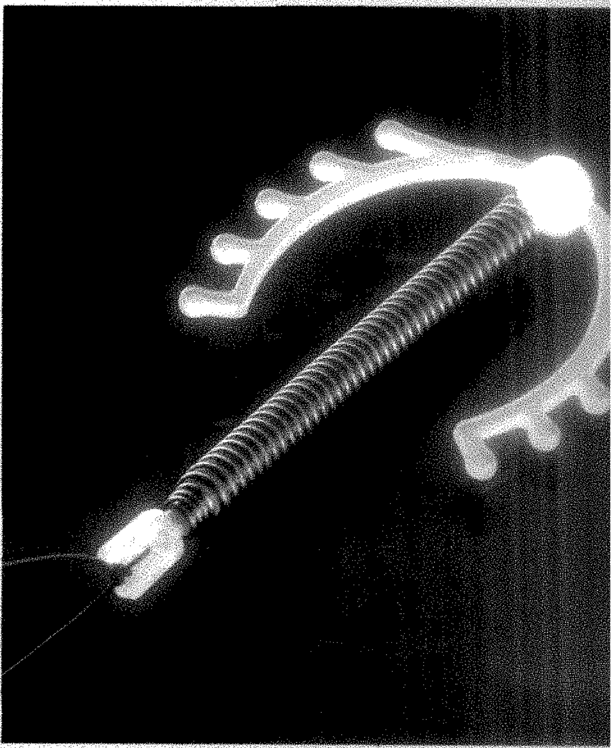

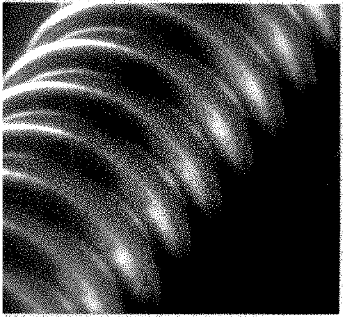

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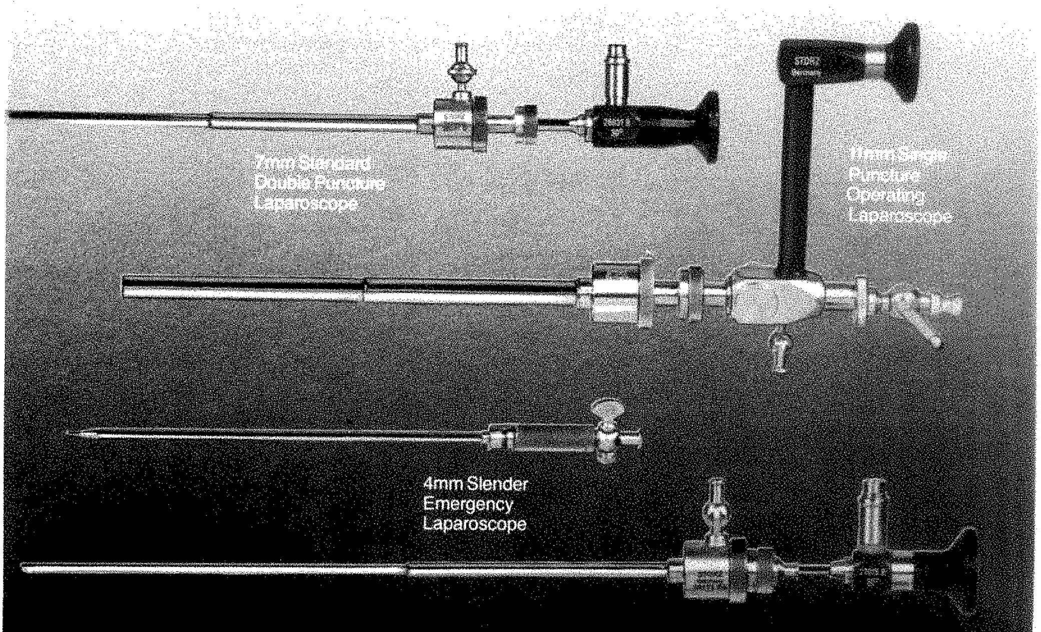
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COMMENTARY

The need for collaboration in randomized controlled trials

There is merit in assessing suggestions for new treatments in well-controlled studies before views on therapy become fixed. It has been argued by Thomas Chalmers (1975) that from scientific, ethical and practical standpoints, exploration of any new therapy should begin with randomization into either conventional or the new treatment regimen. Perhaps if this were done more often, treatments would not be used for decades before being properly evaluated.

For many years progestogens have been recommended as part of the primary treatment of endometrial carcinoma (Taylor 1979). Indeed it has been claimed (on the basis of a single case report) that younger patients with endometrial carcinoma can be cured by following radical surgery with adjuvant therapy with progestogens (Thornton *et al.* 1985). Soon after claims about the value of progestogen therapy in association with surgery and radiotherapy for endometrial carcinoma began to influence clinical practice, Macdonald and his colleagues in Yorkshire decided to assess the validity of the claims in a randomized controlled trial. Their findings were reported in a recent issue of the Journal (Macdonald *et al.* 1988).

Overall 23 gynaecologists, 16 pathologists, eight radiotherapists and 429 women collaborated in the study. Of the 214 women randomized to receive progestogens, 73% were alive 5 years after primary treatment compared with 80% of the women who did not receive the adjuvant drug. The authors conclude that there is no good evidence to support the widespread clinical practice of giving progestogens as part of the primary treatment of endometrial cancer.

Thirty years ago another MacDonald (1957), and Shirodkar (1960), introduced operations for the surgical treatment of cervical incompetence. They both reported that the operation improved the outcome of pregnancy in women who had previously experienced either miscarriages during the second trimester or spontaneous preterm labour and delivery. Although these operations have been used widely since that time, opinions among obstetricians continue to vary both about the criteria for diagnosing cervical incompetence, and about the indications for cervical cerclage. When the Medical Research Council's Working Party on Preterm Labour conducted a survey of British obstetricians it found that some obstetricians never used the operation while others performed cerclage in up to 80 women for every 1000 giving birth under their care.

These dramatic differences in practice suggested the need for a randomized trial to assess the effects of the operation, and so the MRC and the College collaborated to mount the study. Over 200 obstetricians and more than 1000 women in nine countries have collaborated in the MRC/RCOG Cervical Cerclage Trial. A report based on an interim analysis of 905 completed records is presented in this issue of the Journal (p. 437). The results suggest that cervical cerclage may lead to a useful (20%) reduction in the frequency of very preterm delivery (less than 33 completed weeks gestation), but the confidence intervals around this point estimate of the operation's effect make it clear that it could be either substantially more or substantially less than this. Nevertheless, the trial's results constitute the strongest evidence so far available that the operation is effective in at least some of the women in whom it is used: the figures suggest that about 1 in 20 women selected for cerclage in this trial had their pregnancy usefully prolonged.

The results of both these collaborative trials have generated information that is of use to practising obstetricians and gynaecologists and their patients. They have substantially narrowed the range of clinical uncertainty that obviously exists about the effects of the two treatments studied. Proper evaluation of any treatment implies studying sufficient numbers of patients to obtain results which are clear enough to guide clinical practice. As the two studies reviewed here illustrate clearly, this will often imply very widespread collaboration among clinicians. Herein lies a major problem with randomized controlled trials. Because it is often difficult to recruit sufficient patients in a reasonable time, it is possible that the treatment under scrutiny may be superseded by the time the trial is finished. Those who have collaborated in the studies referred to here are to be commended for helping to produce evidence of relevance to all gynaecologists and obstetricians. Clearly, however, if other clinicians had collaborated, neither trial would have taken as long as it did to recruit the samples which were analysed, and more precise estimates of the effects of adjuvant progestogens and cervical cerclage would have been obtained.

Without collaboration on the sort of scale which has become commonplace in some areas of oncology and cardiovascular medicine, obstetricians and gynaecologists are missing opportunities to establish a more scientific foundation for their practice. These two collaborative trials make it clear that widespread collaboration in confronting questions about the effects of different clinical practices in our speciality is possible. They pose a challenge to all practising obstetricians and gynaecologists to look for future opportunities to collaborate in seeking prompter and better answers to the many questions about the effects of our practice.

The number and quality of collaborative trials in obstetrics and gynaecology would be enhanced by the formation of Trials Units comparable to those available to oncologists and cardiologists, and it is to be hoped that the proposed Perinatal Trials Service in Oxford will come to fruition.

Professor Sir Malcolm Macnaughton
Department of Obstetrics and Gynaecology
Glasgow Royal Infirmary
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References

Chalmers, T. C. (1975) Randomization of the first patient *Med Clin North Am* **59**, 1035-1038.

MacDonald, I. A. (1957) Suture of the cervix for inevitable miscarriage *J Obstet Gynaecol Br Emp* **64**, 346-350.

Mcdonald, R R., Thorogood, J. & Mason, M. K (1988) A randomized trial of progestogens in the primary treatment of endometrial carcinoma. *Br J Obstet Gynaecol* **95**, 166-174.

MRC/RCOG Working Party on Cervical Cerclage (1988) Interim report of the MRC/RCOG multicentre randomized trial of cervical cerclage. *Br J Obstet Gynaecol* **95**, 437-445

Shirodkar, V M. (1960) *Contributions to Obstetrics and Gynaecology,* Churchill Livingstone, Edinburgh, pp 1-16.

Taylor, R.W. (1979) Gynaecological malignancy. *Practitioner* **222**, 195-201.

Thornton, J J , Brown, L. A., Wells, M & Scott, J. S. (1985) Primary treatment of endometrial cancer with progestogen alone. *Lancet* **ii**, 207-208.

Without due care

The Medical Defence Union has a film it shows by that title—and very comforting it is. Replete with careless doctors who leave swabs behind and take off the wrong leg, it paints a picture that reassures us all. It is comprehensible. All will be well in the best of all worlds provided you make sure that you get the operating list right and do not allow yourself to be harassed by those officious nurses. You can ensure that litigation is a remote, alien concept. At least, that was the way it looked before Whitehouse *vs* Jordan came along and learned men put their minds to the meaning of words such as 'undue force' and they forgot what it was like to be in the front line making judgments that nearly always worked but occasionally came to grief.

In the November issue of the *American Journal of Obstetrics and Gynecology,* there is an advertisement for an advisory group, the purpose of which is 'to help lead a national effort to resolve the medical professional liability crisis'. One in six obstetricians/gynaecologists in the USA is sued each year, a figure that has risen from 1 in 20 only 10 years ago. Under the heading of 'Endangered Species', the advertisement states that 'the inflation of liability insurance premiums has plunged the obstetric specialty into a crisis situation'. In this issue of the Journal (pp. 454–461) Lois Quam and her colleagues have drawn attention to the differences between the American and British legal systems and at first glance, these considerations should assuage our fears. The problem is that we do not have enough data at the present time to be able to analyse trends. The Medical and Dental Defence Union of Scotland does not necessarily reflect the activities of the two large defence societies in England, although this may only be a matter of time. The only firm indication that we have that all is not well is the exponential rise in subscriptions that has occurred over the last 10 years. We have been extremely well supported by our defence organizations who have given unlimited cover for a modest fee and a wide range of advice on various medico-legal matters. Furthermore, this cover is continued after retirement. The defence organizations in the UK are not insurance companies, but like their American insurance counterparts, they are dependent on reinsurance through the City of London. They are non-profit-making organizations for the mutual protection of doctors and dentists. They are, however, obliged to take account of their members' views. Inevitably, the higher the subscriptions, the greater the incentive will be for large groups of low-risk members to press for differential subscriptions. Even now, the present rates constitute a serious disincentive to doctors undertaking part-time work. The government may itself choose to pay the subscriptions, either as a specified item or by incorporation of the subscription into the overall salary, but if this particular pathway is chosen, it may produce an avalanche of claims which the defence organizations would probably prefer to settle, wherever reasonable, to reduce legal costs and to cope with the high tide of litigation. If nothing is done, and differential subscriptions are introduced, then obstetricians will be in the front line under attack. It could be argued that our specialty tends to have higher incomes than most other disciplines and could, therefore, absorb the cost. That argument would only be valid if the higher subscriptions related only to private practice obstetrics as it would hardly be fair to ask obstetricians to finance their own high-risk situation within the National Health Service. One thing that can be said for certain is that unless there is some financial recognition of this situation, it will be impossible for all full-time National Health Service and academic obstetricians to practise because their occupation would not be economically viable. The problems could certainly not be forced onto the midwives unless the health authorities were prepared to take on the settlement costs for all obstetric cases—a prospect that would hardly be of benefit to their funds in these difficult times. So far, it is likely that the issue of the effect on recruitment has been obfuscated by the common subscription and for this reason it is unlikely that litigation has had any significant adverse effect on recruitment. It may already have had some effect on decisions concerning early retirement and a desire for clinicians to withdraw from obstetrics in favour of gynaecology, and these are matters of concern, but the real issues will not surface until financial discrimination occurs.

The Department of Health and Social Security has already formed a working party to investigate the general problem of medical litigation. It is essential that the working party is properly appraised of what is happening both in the context of the financial implications and in relation to the resolution of liability. The expectation that any Government will establish a no-fault compensation scheme is probably unrealistic because of the financial implications, and in any case, this would not obviate the possibility of further legal action.

The expensive claims in obstetrics are those that relate to surviving but cerebrally abnormal infants. Many of these infants are abnormal for reasons other than the processes of parturition but if there is any abnormality of the fetal heart rate in labour, it is likely that the obstetrician will be at risk on the basis of *res ipsa loquitur*. However, the issues of fault are no longer particularly relevant to the financial implications. At the present time, settlements for individual 'brain damage' cases approach the £1 million mark. It would not be unrealistic to estimate that some error could be made in one patient in a unit delivering 5000 women every year. That would mean that each year there would be 100 to 150 cases where most practitioners would agree that the level of practice was substandard and settlement was the only answer. The total subscription income of the defence organizations would be subsumed on brain-damaged infants. The situation is made even more dangerous by the shadow of the 21-year 'tail' that applies to obstetric cases.

These are matters of grave importance to the future of maternity services and the thoughtful paper by Quam and her colleagues provides some valuable insights into a rapidly changing scene.

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Interim report of the Medical Research Council/Royal College of Obstetricians and Gynaecologists multicentre randomized trial of cervical cerclage

MRC/RCOG WORKING PARTY ON CERVICAL CERCLAGE

Summary. Overall 905 pregnant women whose obstetricians were 'uncertain' whether to recommend cervical cerclage, chiefly because of a history of early delivery or cervical surgery, were randomly allocated to cerclage or no surgery; 92% were treated as allocated. The overall preterm delivery rate was 30%. The results for those allocated cerclage were marginally statistically significant, more favourable in terms of fewer deliveries before 33 weeks [59 (13%) compared with 82 (18%), $P = 0{\cdot}03$] and correspondingly for birthweight under 1500 g [48 (11%) compared with 73 (16%), $P = 0{\cdot}01$] and for miscarriage, stillbirth or neonatal death [37 (8%) compared with 54 (12%), $P = 0{\cdot}06$]. There were similar numbers of deliveries between 33 and 36 weeks [65 (14%) compared with 64 (14%)]. These results suggest that the operation had an important beneficial effect in one in 20 to 25 cases in the trial. But because the observed differences are not strongly statistically significant and because no such benefit has been seen in other randomized trials, there remains uncertainty about how much (if any) of this apparent benefit is real. So, the trial still remains open for randomization of more women whose obstetricians are uncertain about the advisability of cerclage.

The basis for the operation of cervical cerclage is the possibility that a congenital or traumatically acquired weakness of the cervix, or the unusual physiological circumstance of multiple pregnancy, may cause premature dilatation of the cervix, 'cervical incompetence', leading to second trimester miscarriage or preterm delivery.

There is no truly diagnostic test for 'cervical incompetence'. The decision to insert a cervical suture is most commonly based on past obstetric history and, to a lesser extent, clinical assessment of the cervix during pregnancy by vaginal examination. Past obstetric history is not, however, a strong predictor of subsequent early delivery. About 85% of women who have had one previous delivery at 20–36 weeks gestation will carry a subsequent pregnancy to term Even after two such events the term delivery rate is

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MRC/RCOG Working Party on Cervical Cerclage
M. C MACNAUGHTON *Chairman*
I G. CHALMERS
G. V. P. CHAMBERLAIN
V. DUBOWITZ
P. M. DUNN
A. M. GRANT
K McPHERSON
J F PEARSON
R PETO
A. C TURNBULL

Correspondence: Dr A. M. Grant, National Perinatal Epidemiology Unit, Radcliffe Infirmary, Oxford OX2 6HE

still as high as 70% (Bakketeig *et al.* 1979; Carr-Hill & Hall 1985).

Difficulties in making a confident diagnosis of cervical incompetence are reflected in a wide variation in the use of cervical cerclage. Rates reported by British obstetricians in a postal survey in 1979 ranged from zero to 8% pregnancies managed (MRC Working Party on Preterm Labour, unpublished data). The other important reason for this variation is the lack of satisfactory evidence concerning the efficacy of cervical cerclage and the fact that the operation may entail hazards (Rush *et al.* 1984; Lazar *et al.* 1984; Grant 1986, 1988).

The aim of the MRC/RCOG Cervical Cerclage Trial (Macnaughton 1981; Grant 1981–1985) was to assess whether cervical cerclage in women deemed to be at increased risk of cervical incompetence does indeed prolong pregnancy and thereby improve fetal and neonatal outcome. This preliminary report of the trial presents the results of a prespecified interim analysis performed in the autumn of 1986 and presented at the third meeting of trial collaborators in January 1987.

Patients and methods

The trial has involved 200 obstetricians in nine countries. It was supervised by the MRC/RCOG Working Party on Cervical Cerclage and co-ordinated by the National Perinatal Epidemiology Unit in Oxford.

Recruitment started in 1981 and this preliminary report describes the 905 cases with complete records available for analysis in November 1986. Of these 905 women 690 were recruited in the UK, 68 in Norway, 57 in Italy, 31 in France, 29 in Belgium, a further 30 in South Africa, Ireland, Iceland, the Netherlands and Canada. The design of the trial was 'pragmatic' (Schwartz *et al.* 1980). A woman was eligible for entry to the trial if her obstetrician was uncertain whether to advise her to have cervical cerclage. Most women were entered and assigned a random allocation by telephone; a few were registered by post. Most obstetricians used the randomization service provided by the Clinical Trial Service Unit in Oxford, but other randomization centres were established in Italy (Istituto Mario Negri, Milano), Zimbabwe (Harare Maternity Hospital) and Hungary (University Department of Obstetrics, Debrecen). Clinical practice in respect of cerclage is sufficiently different in Hungary for these latter cases not to have been included in this report.

Once basic identifying and descriptive data had been given over the telephone a random allocation was made to one of two clinical policies: either a recommendation to insert a cervical suture (unless some clear contraindication to it arose) or a recommendation to avoid suture (unless a clear indication arose). The treatment allocation was only issued when all those data had been recorded, and once it had been given the woman was irrevocably in that trial group, even if the allocated treatment was not followed. Thus the main analysis is based on the groups as allocated (Peto *et al.* 1977), comparing the policy of cervical cerclage if possible, with the policy of no cerclage unless clearly indicated. Randomization was organized in balanced blocks, but no prognostic stratification was used. The type of operation was not prespecified and was left to the obstetrician responsible for care. A request was made to keep ancillary treatment with betamimetics and bed-rest to a minimum for all women, otherwise subsequent care was left entirely to the clinician responsible. No special tests or special follow-up were required. Outcome of pregnancy was described on a straightforward, single-page, A4-sized questionnaire which was completed by the obstetrician after delivery and sent to the co-ordinating centre for coding and analysis. The prime measures of outcome were length of pregnancy, specifically deliveries before 33 completed weeks and deliveries 'preterm' (i.e. before 37 completed weeks), and the vital status of the baby at the time of completion of the form. A supplementary question on postpartum pyrexia was added after the first 360 women had been entered.

The trial protocol was approved by the ethics committees of the many participating hospitals. Most committees left the nature and timing of the information given to potential participants up to the obstetricians involved. A few committees considered that post-randomization consent was unethical and insisted on pre-randomization consent; a few judged the opposite. One committee refused to approve the trial.

An intention to perform an interim analysis when about 1000 women had joined the trial was specified in the trial protocol. This is the reason for the analyses reported here.

The χ^2 and Student's *t*-tests were used as appropriate. The primary analyses were based on the total trial groups as randomly allocated. Secondary analyses were conducted within six prespecified mutually exclusive strata, characterized by obstetric and gynaecological history.

Results

Table 1 describes the two trial groups at entry: 95% were recruited before 20 completed weeks gestation, the latest gestation at entry being 29 weeks. As expected, the reasons for uncertainty about the advisability of cervical cerclage varied, but 74% of the women had a past history of one or more second trimester miscarriages or preterm deliveries. In addition, 11% had a history of previous surgery to the cervix; in the remaining women cerclage was considered on the basis of other indications such as previous termination of pregnancy, previous first trimester miscarriage, cervical abnormality on physical examination, uterine abnormality or twin pregnancy. Some women had more than one possible reason for considering cerclage. Because of this, the women have been grouped into the six mutually exclusive subgroups (A–F at the bottom of Table 1).

Of those women allocated 'cervical cerclage' 92% actually had a suture inserted, a further 3% miscarried before insertion (Table 2). Of those allocated 'no cerclage' 7% actually had a suture, the most common reason being a clinical judgement after entry that the cervix was opening. In both groups a request from the woman was the other most common reason for not following the trial allocation.

Myometrial depressants and hospital bed-rest were used more often in the cerclage group. The difference in the pattern of hospital admissions was chiefly explained by the extra admissions associated with stitch insertion and stitch removal (Table 2). The onset of labour and mode of delivery were similar in the two groups. Although there were more emergency caesarean sections in the cerclage group (42 compared with 31) this difference was not statistically significant.

Delivery tended to be later in the cerclage group (Fig. 1). Fifty-nine (13%) women in the cerclage group compared with 82 (18%) in the control group were delivered before 33 completed weeks gestation. But this difference was only marginally significant ($P = 0{\cdot}03$), so the results are compatible with both a halving of the rate and no effect: estimated relative risk 0·7, 95% CI 0·5 to 1·0 (Table 3). Similar numbers of women were delivered between 33 and 36 weeks so the preterm delivery rates (27% compared with 32%) also differed by 5%. Nine women in the cerclage group and five in the control group miscarried in the first trimester. Cerclage would not normally be considered in these cases and none had actually been managed with a cervical suture. The distribution of birthweights [48 (11%) compared with 73 (16%) <1500 g, $P = 0{\cdot}01$] mirrors the difference in gestational age at delivery, as does the number of miscarriages, stillbirths and deaths following live birth [37 (8%) compared with 54 (12%), $P = 0{\cdot}06$]: relative risk = 0·7, 95% CI 0·5 to 1·0 (Table 3).

'Any adverse events possibly or probably attributable to suture' were reported in 74 of the 450 women (16%) actually managed with cervical cerclage. No comparable data are available for women who did not have a suture and almost all these events were too non-specific to be attributed to the operation with any confidence. The exceptions to this were trauma to the cervix and stitch removal difficulties, both of which were reported in 6 (1%) women. Puerperal pyrexia of more than 38°C was reported for 15 of 276 women (6%) allocated to cerclage and 8 of 266 (3%) allocated no cerclage but this difference is not conventionally statistically significant.

The results of secondary analyses in the six subgroups in respect of the three main outcome measures are summarized in Table 4. Such subgroup analyses are prone to wide statistical fluctuations, especially when, as here, the overall treatment effect is only marginally significant (Peto 1982). Nevertheless, the protective effect of cervical cerclage (if it exists) does appear to be concentrated in the groups characterized by a previous early delivery and does appear to increase as the number of previous early deliveries increases.

Although there is no evidence of a beneficial effect in the cases characterized by previous surgery to the cervix, these estimates are based on small numbers and are compatible with both an important beneficial effect and an important adverse effect of cervical cerclage.

Discussion

The impetus behind the MRC/RCOG Cervical Cerclage Trial was recognition of the high mor-

Table 1. Description of the trial groups at entry

	Cerclage ($n = 454$)	No cerclage ($n = 451$)
Maternal age (years) mean [SD]	27·5 [6·1]	27·5 [4·8]
Gestational age (weeks) at entry mean [SD]	13·7 [3·5]	14·2 [4·2]
Previous preterm deliveries* *n* (%)		
0	257 (57)	270 (60)
1	144 (32)	135 (30)
2–4	52 (11)	42 (9)
≥5	1 (0)	3 (1)
Previous second trimester miscarriages* *n* (%)		
0	239 (53)	242 (58)
1	178 (39)	166 (37)
≥2	37 (8)	42 (9)
Previous early miscarriages* *n* (%)		
0	317 (70)	312 (69)
1	92 (20)	76 (17)
≥2	45 (10)	62 (14)
Previous induced abortions* *n* (%)		
0	325 (72)	326 (72)
1	91 (20)	87 (19)
≥2	38 (8)	37 (8)
Previous preterm delivery *or* second trimester miscarriage* *n* (%)		
0	107 (24)	125 (28)
1	230 (51)	208 (46)
2–3	101 (22)	98 (22)
≥4	16 (4)	19 (4)
Past cervical history* *n* (%)		
Cone biopsy	39 (9)	37 (8)
Cervical amputation	11 (2)	19 (4)
Previous cervical suture	94 (21)	84 (19)
Other indications* *n* (%)		
'Abnormal' cervix	43 (10)	62 (14)
Uterine abnormality	12 (3)	7 (2)
Twins	10 (2)	14 (3)
Others	18 (4)	9 (2)
Mutually exclusive subgroups *n* (%)		
(A) Singletons with one second trimester miscarriage or preterm delivery in the past (no surgery to the cervix)	215 (47)	198 (44)
(B) Singletons with two second trimester miscarriages or preterm deliveries in the past (no surgery to the cervix)	70 (15)	68 (15)
(C) Singletons with three or more second trimester miscarriages or preterm deliveries in the past (no surgery to the cervix)	40 (9)	39 (9)
(D) Singleton, previous cone biopsy or cervical amputation	46 (10)	50 (11)
(E) Singletons with other indications	73 (16)	82 (18)
(F) Twin pregnancies	10 (2)	14 (3)

* Entry details are not available for one woman

Table 2. Clinical management of trial groups

	Cerclage ($n = 454$)	No cerclage ($n = 451$)
Actual use of cervical suture *n* (%)		
Suture inserted	417 (92)	33 (7)
No suture	37 (8)	418 (93)
Reasons for non-compliance *n* (%)		
(A) Allocated suture—no suture inserted		
Patient's request	21 (5)	
Miscarriage before insertion	13 (3)	
Other	3 (0)	
(B) Allocated no suture—suture inserted		
Patient's request		10 (2)
Cervix opening		21 (5)
Misheard allocation over telephone		1 (0)
Not known		1 (0)
Myometrial depressants used *n* (%)	133 (29)	107 (24)
Hospital bed-rest *n* (%)	135 (30)	114 (25)
Hospital admissions		
No./patient mean [SE]	1·5 [0·05]	0·6 [0·05]
Total length stay antenatally (days) mean [SE]	9·0 [0·5]	5·9 [0·6]
Total length stay antenatally excluding time for suture (days) mean [SE]	5·1 [0·5]	5·5 [0·6]
Total length of stay postnatally (days) mean [SE]	5·9 [0·2]	5·5 [0·2]
Onset of labour—spontaneous *n* (%)	338 (74)	350 (78)
Mode of delivery *n* (%)		
Spontaneous cephalic	333 (73)	346 (77)
Instrumental	40 (9)	38 (8)
Emergency caesarean	42 (9)	31 (7)
Elective caesarean	26 (6)	25 (6)
Vaginal breech	10 (2)	6 (1)
Not known	3 (1)	5 (1)

Table 3. Fetal and neonatal outcome

	Cerclage ($n = 454$)	No cerclage ($n = 451$)
Gestational age at delivery (weeks) *n* (%)		
<13	9 (2)	5 (1)
13–32	50 (11)	77 (17)
33–36	65 (14)	64 (14)
≥37	330 (73)	305 (68)
Mean [SE]	36 3 [0·3]	35·7 [0 3]
Birthweight (g) *n* (%)		
<1500	48 (11)	73 (16)
1500–2499	70 (15)	66 (15)
Vital outcome *n* (%)		
Liveborn, survived	417 (92)	397 (88)
Liveborn, died	4 (1)	12 (3)
Stillbirth or miscarriage	33 (7)	42 (9)

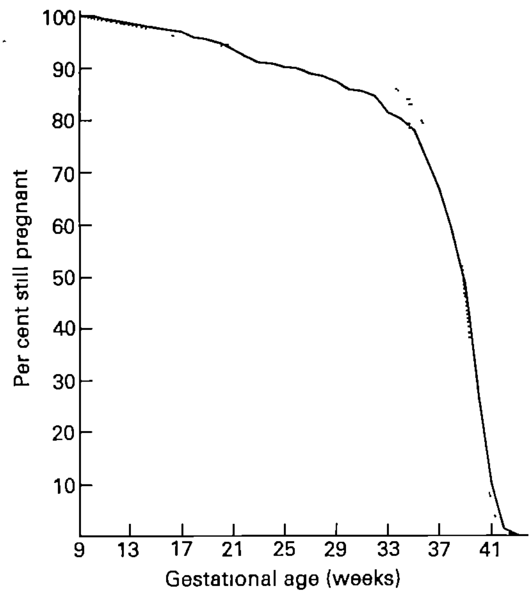

Fig. 1. Timing of delivery in two trial groups: per cent still pregnant at end of a week in pregnancy – – –, Cerclage; ——, no cerclage

tality and morbidity associated with preterm delivery (Rush *et al.* 1976, Verloove-Vanhorick *et al.* 1986). Cervical cerclage was identified as a strategy for prevention, which had been poorly assessed. It was recognized that in rare cases the operation may have serious adverse effects and that there was no good evidence of its efficacy. Uncertainty about the place of the operation was confirmed in a survey conducted by the MRC/RCOG Working Party on Preterm Labour in 1979 (unpublished observations), which revealed extraordinarily wide variation in the use of the procedure by British consultant obstetricians. This variation was one of the reasons for the choice of relatively flexible entry criteria. There was no possibility of consensus about where the uncertainty lay. Furthermore, it was argued that cases which would meet more rigid entry criteria would be entered into a trial with more open criteria by those obstetricians whose uncertainty happened to coincide with the rigid criteria. The advantage of this strategy was that other types of cases for which other obstetricians were uncertain about the

Table 4. Outcome in six prespecified subgroups

	Delivery before 33 completed weeks *n* (%)	Delivery before 37 completed weeks *n* (%)	Miscarriage, stillbirth or death following livebirth *n* (%)
All cases			
Cerclage (*n* = 454)	59 (13)	124 (27)	37 (8)
No cerclage (*n* = 451)	82 (18)	146 (32)	54 (12)
Singletons, 1 STM or PTD			
Cerclage (*n* = 215)	31 (14)	59 (27)	15 (7)
No cerclage (*n* = 198)	34 (17)	58 (29)	23 (12)
Singletons, 2 STM or PTD			
Cerclage (*n* = 70)	10 (14)	18 (26)	8 (11)
No cerclage (*n* = 68)	14 (21)	25 (37)	12 (18)
Singletons, 3 or more STM or PTD			
Cerclage (*n* = 40)	2 (5)	11 (28)	2 (5)
No cerclage (*n* = 39)	13 (33)	22 (56)	6 (15)
Singletons, cone biopsy or cervical amputation			
Cerclage (*n* = 46)	9 (20)	16 (35)	8 (17)
No cerclage (*n* = 50)	10 (20)	15 (30)	7 (14)
Singletons, other indications			
Cerclage (*n* = 73)	6 (8)	14 (19)	3 (4)
No cerclage (*n* = 82)	7 (9)	19 (23)	5 (6)
Twins			
Cerclage (*n* = 10)	1 (10)	6 (60)	1 (10)
No cerclage (*n* = 14)	4 (29)	7 (50)	1 (7)

STM, Second trimester miscarriage, PTD, preterm delivery

Table 5. Summary of results of four published trials of cervical cerclage

	Delivery before 33 completed weeks *n* (%)	Delivery before 37 completed weeks *n* (%)	Miscarriage, stillbirth or death following livebirth *n* (%)
MRC/RCOG interim			
Cerclage ($n = 454$)	59 (13)	124 (27)	37 (8)
No cerclage ($n = 451$)	82 (18)	146 (32)	54 (12)
Rush *et al* (1984)			
Cerclage ($n = 96$)	12 (13)	33 (34)	9 (9)
No cerclage ($n = 98$)	10 (10)	31 (32)	9 (9)
Lazar *et al.* (1984)			
Cerclage ($n = 268$)	4 (1)	18 (7)	2 (1)
No cerclage ($n = 238$)	1 (0·4)	13 (5)	1 (0·5)
Dor *et al.* (1982)			
Cerclage ($n = 25$)	6 (24)	13 (52)	7 (28)
No cerclage ($n = 25$)	5 (20)	14 (56)	6 (24)

advisability of cerclage would be entered into the trial. It was hoped that a wide variety of patients would be randomized and that analysis of patients in six prespecified subgroups would then help to determine who (if anyone) could be expected to benefit from cerclage.

The reasons for considering cervical cerclage for women entered into the trial did indeed vary, although the commonest indication was a past obstetric history of second trimester miscarriage or preterm delivery. The study population was at high risk of early delivery in the index pregnancy as judged by an overall preterm delivery rate of 30%.

The type of operation was not prespecified. There is the possibility of exploring differential benefits and hazards of the two most commonly used techniques—those associated with the names of Shirodkar (1960) and McDonald (1957)—within the context of the MRC/RCOG trial This will be attempted in the final analysis of the study.

Much of the information on possible hazards of cervical cerclage is difficult to interpret because the events are non-specific and no comparable information is available for the control group. There was no clustering of miscarriages around the time of cerclage insertion—if anything the clustering occurred in the no-suture group—suggesting that miscarriage caused by the operation is not a common hazard. There is a suggestion of an association between emergency caesarean section and cervical cerclage and further details of these cases will be sought, to ascertain whether or not this difference reflected failure of the cervix to dilate during labour. An alternative explanation is a greater willingness to perform caesarean section for other reasons because of increased fetal maturity associated with cerclage. Puerperal pyrexia was twice as common in the cerclage group and this supports the findings of Rush *et al.* (1984)

Since the MRC/RCOG trial was established, three smaller randomized controlled trials comparing cervical cerclage with conservative management have been reported (Dor *et al.* 1982; Rush *et al.* 1984; Lazar *et al.* 1984) and these have been reviewed elsewhere (Grant 1986, 1988). With the possible exception of Rush's study of singleton pregnancies with an overall preterm delivery rate of 33%, these trials have limited applicability to discussion of the MRC/RCOG trial. Dor investigated twin pregnancies only; Lazar recruited women with singleton pregnancies with an overall preterm delivery rate of only 6%. Nevertheless, the results of previously reported trials are consistent with those of the MRC/RCOG trial in suggesting increased obstetric intervention as judged by admission to hospital, the use of oral betamimetics, induction of labour and caesarean section. The MRC/RCOG trial differs from the other trials in its suggestion of a beneficial effect of cerclage on length of gestation and vital outcome (Table 5). There were 5% fewer deliveries between 20 and 32 weeks gestation, which, if real, would be equivalent to the prevention of one preterm delivery for every 20 sutures inserted. The result is of only marginal statistical significance, however, and is compatible with a wide range of possible effects of the operation on the occurrence of delivery before 33 weeks. The difference in the timing of delivery was reflected in improved survival. Additional information about the babies who died will be sought to explore this relation further.

The relatively small numbers of women in the subgroups limit the reliability of the secondary stratified analyses. The difference in outcome did, however, appear to be concentrated in the subgroups characterized by previous early deliveries and to increase with the number of early deliveries experienced in the past. But some, at least, of this pattern is due to the play of chance. An indication of this is the low rate of delivery before 33 weeks in the cerclage group with the poorest obstetric history (2 of 40, 5%) compared with those with a relatively good history (41 of 285, 14%). Overall, there must remain uncertainty as to whether any real benefit has yet been demonstrated in any category of women. Those obstetricians who, in the light of this interim report, remain uncertain about the advisability of cervical cerclage for some women under their care can, if they wish, continue to enter cases into the Cervical Cerclage Trial. Details of the procedures are available from the co-ordinating centre.

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References

Bakketeig, L S., Hoffman, H. J. & Harley, E. E. (1979) The tendency to repeat gestational age and birthweight in successive births. *Am J Obstet Gynecol* **135**, 1086-1103.

Carr-Hill, R A. & Hall, M. H. (1985) The repetition of spontaneous preterm labour. *Br J Obstet Gynaecol* **92**, 921-928.

Dor, J., Shalev, J., Mashiach, G , Blankstein, J & Serr, D. M. (1982) Elective cervical suture of twin pregnancies diagnosed ultrasonically in the first trimester following induced ovulation. *Gynecol Obstet Invest* **13**, 55-60.

Grant, A. (ed.) (1981–1985) MRC/RCOG Randomized Cervical Cerclage Trial Newsletters 1-10. National Perinatal Epidemiology Unit, Oxford.

Grant, A. (1986) Cervical cerclage: evaluation studies. In *Prevention of Preterm Birth New Goals and New Practices in Prenatal Care* (Papiernik, E , Bréart, G. & Spira, N., eds), INSERM, Paris, pp. 83-99.

Grant, A (1988) Cervical cerclage In *Effective Care in Pregnancy and Childbirth* (Enkin, M., Keirse, M J. N. C. & Chalmers, I , eds), Oxford University Press, Oxford (in press).

Lazar, P , Gueguen, S., Dreyfus, J., Renaud, R., Pontonnier, G. & Papiernik, E (1984) Multicentred controlled trial of cervical cerclage in women at moderate risk of preterm delivery. *Br J Obstet Gynaecol* **91**, 731-735.

McDonald, I. A. (1957) Suture of the cervix for inevitable miscarriage *J Obstet Gynaecol Br Emp* **64**, 346-350.

Macnaughton, M. C (1981) MRC/RCOG Cervical Cerclage Trial. *Lancet* **i**, 1320.

Peto, R (1982) Statistical aspects of cancer trials In *Treatment of Cancer* (Halnar, K E , ed.), Chapman & Hall, London, pp. 867-871.

Peto, R., Pike, M. C., Armitage, P *et al.* (1977) Design and analysis of randomized clinical trials requiring prolonged observation of each patient. Part II. Analysis *Br J Cancer* **35**, 1-39.

Rush, R. W., Keirse, M. J. N. C., Howat, P., Baum, J. D., Anderson, A. B M & Turnbull, A C. (1976) Contribution of preterm delivery to perinatal mortality. *Br Med J* **ii**, 965-968

Rush, R W., Isaacs, S., McPherson, K., Jones, L., Chalmers, I. & Grant, A. (1984) A randomized controlled trial of cervical cerclage in women at high risk of preterm delivery. *Br J Obstet Gynaecol* **91**, 724-730

Schwartz, D , Flamant, R. & Lellouch, J (1980) *Clinical Trials.* Academic Press, London.

Shirodkar, V. N (1960) *Contributions to Obstetrics and Gynaecology* Churchill Livingstone, Edinburgh, pp 1-16

Verloove-Vanhorick, S. P., Verwey, R A , Brand, R , Bennebroek-Gravenhorst, J. & Keirse, M. J. N. C. (1986) Neonatal mortality risk in relation to gestational age and birthweight. *Lancet* **i**, 55-57.

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Video display terminals and pregnancy. A review

ROLAND BLACKWELL, ALLAN CHANG

Background

The increasing use of computers and word processors has led to widespread anxieties concerning the possible harmful effects of video display terminals (VDTs). The anxiety arises from many published reports of clusters of reproductive failures associated with users of VDTs, the entrepreneurial development of protective devices and garments, and demands by trade unions for alteration of working conditions and for compensation. This paper summarizes informed opinion and evidence available on this issue.

Reports of pregnancy failures amongst VDT users

Clusters of pregnancy failures

At least 20 reports from the Western world have been published of clusters amongst VDT users in which more than 50% of the women in a group have experienced miscarriage and other pregnancy failures. About 12 of these reports are acceptably documented and eight have been the subject of extensive investigation (for detailed reviews see Purdham 1984; Denning 1985; Labour Research Department 1985).

For example, the 'Sears–Roebuck' cluster in Dallas has been followed up in detail by the Centre for Disease Control (Binkin *et al.* 1981). Of 75 workers in one department using VDTs 12 became pregnant, seven of these pregnancies ended in miscarriage and there was one neonatal death, a failure rate of 67%. A control group of 59 workers in a department not using VDTs showed a 15% failure rate ($P<0\cdot0006$). Subsequently there have been four pregnancies in women from the same office, all of them normal (Bergqvist 1986).

Binkin *et al.* (1981) concluded that this was an 'expected-unexpected' cluster, i.e. because clusters are isolated in time and space they may be random chance occurrences rather than indicators of a causal relation. The probability of such events occurring may be estimated. There are tens of millions of VDTs in use (there are in excess of 10^7 in the USA, and the TUC estimate $1\cdot5 \times 10^6$ in the UK). At a conservative estimate there are 20 000 groups of women where at least 10 could become pregnant in one year. A naturally occurring pregnancy failure rate of 15% yields a probability that, by chance, 29 clusters would occur each year in which more than half the pregnant women experienced a failure. Thus the reported levels are explicable (but not dismissable).

Large-scale epidemiological studies

There are more than nine epidemiological studies reported. Only the most recent are of large scale and not all have appeared in the peer review literature. Some have been reported only in the proceedings of major meetings. None of them concludes that there is a causal link between VDT use and pregnancy failure.

Some studies have insufficient statistical power to be useful and others have not observed the established techniques of epidemiology. The four which have not been considered in our review are described in Mackay (1987) and are included in the references for completeness (Lewis *et al.* 1982; Frank 1983, unpublished observations; Kajiwara 1984; Lee & McNamee 1984).

In any epidemiological investigation of scientific value it is necessary to define terms carefully, to consider biases which could influence the study, and to take account of associated vari-

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University College Hospital, London
ROLAND BLACKWELL *Deputy Chief Physicist*

Chinese University of Hong Kong
ALLAN CHANG *Professor of Obstetrics and Gynaecology*

Correspondence: R. Blackwell, Head of Medical Physics, Department of Medical Physics and Bioengineering, University College Hospital, Gower Street, London WC1E 6AU

ables which could be alternative causes of the result ('confounding' factors) (Lee 1985).

Thus, the rates of miscarriage reported by the doctor or the patient or determined by hCG assay may vary widely, so how should the investigator decide that a miscarriage has occurred? Similarly, the reported prevalence of anomalies depends upon the way the question is asked. Defining exposure is almost as difficult. A subject's perception of work conditions, i.e. time spent at a VDT, often differs significantly from reality. The use of occupational classes may give a more reliable indication of time spent at the terminal.

A bias may result from a differing reply rate in the exposed and control groups, a response bias. Also, under-reporting in a control group is a well-known phenomenon. For instance, in a study of miscarriage and exposure to anaesthetic gases, when checked against medical records, the non-exposed group was found to have under-reported miscarriage by 32% whereas the women in the exposed group recalled all miscarriages (Axelsson & Rylander 1982).

Confounding factors are of particular interest in the study of miscarriages. There is good evidence that heavy smoking increases the probability of miscarriage (Himmelberger *et al.* 1978) and the occurrence of a previous miscarriage has been reported to increase substantially the probability of a second (Knill-Jones 1986). Thus, smoking and gravidity must be accounted for. Similarly, maternal age, regular drinking of alcohol, irregular shift work, and other factors are believed to affect the probability of pregnancy failure.

The five studies summarized in Table 1 were chosen because they meet the following criteria: large sample size; appropriate control group; verification of medical and occupational histories attempted; and control for confounding factors.

In all large-scale studies there was no statistically significant association between VDT use and pregnancy failure. Both Kurppa *et al.* (1985) and Westerholm & Ericson (1986) noted slightly more major cardiovascular abnormalities in the case group than in the controls. However, the total numbers of abnormalities were small and the increases were not statistically significant. Follow-up studies on large numbers of cardiovascular abnormalities should show a relation if one exists. There is, as yet, very little reliable data on early fetal losses.

Further studies

There are eight or more major studies under way. Two are of special note. The National Institute for Occupational Safety and Health are performing a retrospective study of 4000 telephone operators in the USA. Long-distance operators do not use VDTs while directory assistance operators do. In all other respects the work is very similar. The proposed programme is extremely thorough and should help provide reliable results. Interviewing started in January 1987.

A prospective cohort study of 3000 intensive VDT users and 3000 non-users has been initiated by the Mount Sinai School of Medicine, NY, USA. This study includes the monthly determination of urinary hCG levels and should provide information on early fetal losses.

Radiation hazards

If an effect exists there must be a mechanism. It has been proposed that radiation from the terminal is hazardous. We discuss here measurements of radiation and standards relating to VDTs.

Recently low voltage solid state displays have been available, emitting little radiation of any sort. However, the vast majority of VDTs in use, and the type concerning us, are essentially television sets. In addition to visible light, electromagnetic radiations of other frequencies are emitted. The radiation emitted is, with few exceptions, so weak that specially sensitive survey instruments have to be used to record any output at all.

There have been over 20 surveys of VDTs covering more than 200 models of terminal, both colour and monochrome. In addition, some of the popular models have been surveyed across many machines. The maximum output levels for each type of radiation found in these surveys, working from the highest frequency of electromagnetic radiations down to static fields, are summarized below.

X-rays

X-rays are produced when the electron beam strikes the screen of the VDT. Since the 1960s, about 50% by weight of the glass used for the VDT envelope has been lead oxide which reduces the already small X-ray leakage to negligible levels. The Ionising Radiation Regulations (1985) give 2·5 μSv h^{-1} as the dose rate limit for

Table 1. Characteristics of five studies on video display terminals and pregnancy outcome

Author (date), Origin, Type	Description of groups	Outcome*	Remarks
Butler & Brix (1986) USA Case-control	A total of 728 mothers working for State of Michigan and aged <40 years given 30-min interview at their workplace where extent of VDT use was verified, 817 pregnancies were appropriate	For >20 h use/week observed to expected ratio for miscarriage = 1·23; not statistically significant (P=0·65)	Primary purpose of questionnaire disguised; no dose-response relation; continuing study, preliminary report only
Ericson & Kallen (1986) Sweden Case-control	Postal questionnaire; 93% response; 522 cases and 1032 controls selected from Swedish birth and hospitalization records; subjects grouped by occupation into high, medium and low VDT usage	After correction for confounders the odds ratio for increase in miscarriage rate was 1·2 for the group using VDTs for >10 h/week; not statistically significant	Job stress and smoking identified as strong co-varying factors for miscarriage
Kurppa *et al.* (1985) Finland Case-control	Consecutive cases drawn from Finnish national birth defects registry matched in pairs with 1475 controls	Fifty-one cases *vs* 60 controls were users; for >4 h use/day there were 31 cases *vs* 31 controls; no significant association	Specific reference to VDT work avoided; 21 cases of cardiovascular abnormality found, 13 in cases and 8 in controls; follow-up study in progress of further 400 cases of cardiovascular abnormality
McDonald *et al.* (1986) Canada Case-control	Hospitalized deliveries (n = 51 885) and spontaneous abortions (n = 4127) questioned before discharge on work, obstetric history, VDT use, and stress factors	Malformed in VDT group was 3·3% *vs* 3·7% in non-user group; rate of miscarriage did not vary significantly with different levels of VDT use	Recall bias believed to be a problem in the analysis of miscarriage; no significant relation between VDT use and congenital malformations
Westerholm & Ericson (1986) Sweden Cohort	Women all worked for Swedish Social Security between 1980 and 1983; retrospective study of 4117 births in National Medical Birth Register and Register of Hospitalized Spontaneous Abortions. Work time at VDT determined in conjunction with trade union	No significant difference in rate of miscarriage between VDT users and other groups; malformations in children of occasional users were 1·9 times as frequent as in non-users group, but there was no elevation of malformations in heavy users group	There were 1·1 times more cardiothoracic malformations observed in user group; total number of observed malformations was small and the increases were not statistically significant

* The 'odds ratio' is the ratio of the number of times the result occurred in the exposed group to the number of times it occurred in the same number of controls.

members of the general public. This figure may ultimately be reduced by a factor of three in the light of recent recommendations from the National Radiological Protection Board (1987). The highest X-ray figure ever reported is equivalent to 3 μSv h^{-1} and is taken from the survey by Murray (1984). It relates to old equipment which was running under deliberately induced fault conditions. This VDT was removed from the market. We have not found a survey on modern equipment which has reported a level above 0·1 μSv h^{-1} (we all live in a background of naturally occurring radiation which has a level of about 0·3 μSv h^{-1}). All recent results indicate that X-rays from modern VDTs can only be detected in specially shielded rooms designed to eliminate the effect of radiation from the ^{40}K isotope occurring naturally in the glass screen (Doerfel *et al.* 1986). Typically, the X-ray dose received from the naturally occurring isotopes in the body of a person sitting next to you (50 cm away) is about five times that received from sitting at the VDT (McKinlay 1986).

Ultraviolet

Ultraviolet radiation is produced along with visible light. The radiation level is usually too low to be detected in the far part of the spectral range. The highest level, reported by Cox (1984), for the near part of the u.v. range is 0·124 W m^{-2}. Most countries in the world, including the UK, have adopted the standard set by the American Conference of Governmental Industrial Hygienists (ACGIH 1986). The standard is complicated, but for the range of interest the limit is equivalent to 10 W m^{-2}. The ultraviolet light exposure received from 2 min outside on a sunny day is the same as that received from 1 month working continuously at a typical VDT.

Visible

VDTs are designed to emit light. The highest output radiance found for blue light (which is thought to be responsible for accelerating eye ageing) is 3 W m^{-2} sr^{-1} recorded by Paulsson *et al.* (1984). The ACGIH limit is 100 W m^{-2} sr^{-1}.

Infra-red

Infra-red radiation is produced by warm components. For both near and far infra-red the highest levels have been recorded by Cox (1984), the near level 4 W m^{-2} and the far 0·05 W m^{-2}. The ACGIH recommends a limit of 100 W m^{-2} for continuous exposure. The infra-red irradiance of a typical VDT is about the same as that generated by a human hand.

Microwaves and radiofrequencies

Microwaves must be considered since nickel-lined aprons are sold to protect operators from this radiation! We have not found any survey where the investigators found a microwave level above background.

Radiofrequency fields are generated by the character generation circuits. In the range 3 MHz–1 GHz the highest level recorded is 0·5 V m^{-1} (Cox 1984). The Canadian standard for the general public, which is lower than European standards (WHO 1981), recommends a maximum level of 60 V m^{-1}.

Very low frequency electric fields

The accelerating voltage for the electron beam is generated by a component called the line transformer. The transformer 'leaks' an electric field at a frequency of about 15–30 kHz. By shielding the transformer, spraying the plastic case of the equipment with an earthed conductive layer, and covering the ventilation holes in the case with metal gauze, the electric field is often reduced to negligible levels. This shielding is not undertaken for safety purposes but to prevent interference with other sensitive electronic equipment which often accompanies the VDT.

The field falls very rapidly with distance from the source (approximately an inverse cube relation). The field at the transformer is hundreds of times that at the case which is, in turn, perhaps ten times higher than that at the position of the operator. A worker seated to the side or back of the terminal, close to the position of the transformer, could receive an exposure slightly higher than the operator, but still well within acceptable limits.

The highest field recorded against the transformer itself is 1·8 kV m^{-1} (Cox 1984). Villforth (1981) of the US Bureau of Radiological Health found a level of 64 V m^{-1} against the case. At the position of the operator these levels will be lower and for shielded equipment very much lower. There is currently no standard in the UK for such fields but the National Radiological Protection Board (1986) published draft proposals for protection of the public from fields at frequencies below 300 GHz. This discussion document takes account of ANSI (1982) and WHO (1984) recommendations and suggests a limit of 800 V m^{-1} in the frequency range 750 Hz–475 kHz Standards in Eastern bloc countries currently recommend much lower values. The USSR standard for continuous exposure in the 30–300 kHz range is 20 V m^{-1} for the general population. Equipment complying with West German FZZ or US FCC standards produces very low fields.

Extremely low frequency magnetic fields

The mains transformer and other components produce a mains frequency magnetic field. The magnetic field which is used to steer the electron beam also produces a range of low frequencies. The level of this radiation is above background and deserves special attention since some workers believe it may be associated with biological effects.

The highest field reported, measured against the flyback transformer, is 33 A m^{-1} (Sharma, reported in Guy 1984) compared to the limit proposed by NRPB (1986) of 38 A m^{-1}. This field also decreases roughly as the cube of the distance. At the casing, Guy reported a level of 0·77 A m^{-1}. For comparison 1-h use of a VDT is roughly equivalent to 1-min use of a food mixer. The magnetic field, although small, is not easy to reduce further. The output transformer is often shielded by a shorted copper strip acting as a single turn around the transformer. However, the beam deflection coils cannot be shielded because the field emanates from the screen itself. In modern designs the power fed to these coils has been substantially reduced with a consequent reduction in the magnetic field. Further reduction results in the clarity of the display falling to unacceptable levels and eye strain is produced.

A changing magnetic field will induce an electric current in the body. The magnitude of the current is related to the time rate of change of the magnetic field rather than its absolute value and this could be regarded as the dominant consideration in respect of safety.

At low frequencies the rate of change magnetic field is measured in Tesla per second (T s^{-1}). The earth's static magnetic field is about 50 mT. The only UK standard (NRPB 1983; Saunders & Smith 1984) relates to MRI equipment in which the rate of change of field is limited to 3 T s^{-1} and the static field to 2 T. Mild (1986) has reported a rate of change of field at the case of a terminal as high as 350 mT s^{-1} although typically the rates were less than 10 mT s^{-1}.

Bioeffects of extremely low frequency magnetic fields

At static magnetic field intensities of some thousands of Tesla electrical activity across cell membranes and within the cell may be disrupted and studies have demonstrated that cell growth and some enzyme activities may be inhibited. The effect of high intensity electromagentic fields on the developing embryo is not clear.

Some workers believe that even at low intensities biological effects may occur. A number of animal investigations have been carried out, some apparently with positive results. The evidence is as follows.

Chick eggs

Delgardo *et al.* (1982) placed chick eggs in a Helmholtz coil in an incubator for 48 h and found an increased frequency of malformations in the exposed eggs compared with controls in the same incubator. Mild (1986) pointed out that, as effective shielding was not present, interpretation of the result was difficult since the applied field also passed around the outside of the coil and through the control eggs.

Ubeda *et al.* (1983) continued this work using a long cylindrical coil to produce the field. They calculated the field and found that developmental abnormalities, particularly of the nervous system, only occurred when the field intensity was pulsed at a frequency of 100 Hz and with an amplitude of 1·2 μT. Below and above these values the results were negative. They suggested a 'window' effect.

Neither Mild (1986) nor Maffeo *et al.* (1984) using pulsed fields over the range reported by Ubeda *et al.* (1983) could find a positive result. Mild (1986) reported that, when a coil similar to that used by Ubeda *et al* was driven with the waveform described, measurements of the field within the coil showed that it acted as a short-circuited transmission line which resonated to produce a 14–46 kHz field of uneven intensity both across the coil and through its length. This finding casts doubt on the meaning of the results published by Ubeda *et al.* (1983).

Juutilainen *et al.* (1986) exposed eggs to a variety of waveforms and concluded that, with bipolar pulses and a threshold of 1 μT, there was an increase in abnormality rate of up to 56%. However, a number of other variables were not controlled and Sandstrom (1986) considered that a variable and prolonged time before the embryo was examined was a major weakness in the technique.

All of these results are equivocal. Five independent laboratories have agreed to co-operate in an international multicentre study using identical apparatus and protocol to try to resolve the situation.

Rats and mice

Mikolajczyk *et al.* (1986) repeatedly exposed a total of 19 pregnant rats 30 cm from monochrome and colour TVs mounted above the animals. They observed a lower average birthweight in the offspring of the exposed animals, but the numbers were far too small to show statistically significant differences.

Tribukait *et al.* (1986) have published a preliminary report on investigations of pregnant C3H mice exposed to low intensity magnetic fields of between 1 and 15 μT. The mice were exposed from days 0 to 14 in five groups of between 40 and 60 animals and the offspring examined. There were no differences in weight or resorptions but there were 1·9% external abnormalities in the 15 μT-exposed group compared with 0·2% in the controls. However, historical controls have a much higher abnormality rate of 0·8% and the authors concluded that the experiment was deficient in the number of animals studied so that it was impossible to draw definite conclusions. Their investigation has been extended but has not yet been reported.

Mild (1986) calculated that, if confirmed, the effects on animal embryos are caused by induced current densities of well above 10 mA m^{-2}. To induce similar currents in man, the required rate of change of the field in the body is greater than 400 mT s^{-1}, which is at least an order of magnitude above that produced by a typical VDT.

Research is continuing in this area and results based on reliable techniques should soon be available. However, it seems reasonable to assume that the intensity and frequency of electromagnetic radiation around modern VDTs is unlikely to affect the developing human embryo.

Static electric fields

With use, a VDT screen may acquire a static charge. A field of 30 kV m^{-1} was measured by Paulsson *et al.* (1984). A study by Olsen (1981) of 29 VDTs and 78 operators showed that at the position of the operator 95% experienced a field less than 300 V m^{-1}. Biological effects have been observed in fields of more than 100 kV m^{-1} (Dubrov *et al.* 1968). These fields are not thought to be hazardous to the embryo which is in an equipotential environment. It has been suggested that very high fields may be sufficient to drive microscopic dust particles towards the face of a VDT user and sensitive skin may exhibit a rash (Nilsen 1982). Modern screens are coated with an earthed 'bloom' which minimizes both static and reflection of ambient light. Static can be eliminated by the use of a transparent earthed screen shielding the VDT screen.

Environmental and stress factors

Factors other than electromagnetic radiation have also been investigated. Airborne ultrasound at low levels is generated (68 dB was reported by Villforth (1981)). It has been suggested that there may have been the release of minute amounts of polychlorinated biphenyls (PCB) from early equipment (the use of PCBs in electronic components has been forbidden in some countries for the past decade). It is also suggested that an excess of light air ions may be produced, although there is no strong evidence for this (Bergqvist 1984*a*, *b*).

Job stress and operator posture have both been implicated and certainly cannot be entirely dismissed (Mackay 1987). Studies have shown variable increases in eye strain, headache, irritability and sleeplessness in VDT users, compared with users of other office equipments. It has been suggested that VDT users require greater concentration, and are subjected to greater stress which in turn may adversely affect pregnancies. Prolonged sitting, often with poor posture, may be unwise. However, the exact nature of any stresses and any accompanying physiological changes which may affect pregnancy, have not so far been defined.

Conclusions

Recent epidemiological evidence has not demonstrated a statistically significant association between pregnancy failure and the use of VDTs. If there is an effect it is certainly very much smaller than suggested by those who extrapolate to all users from the levels occurring in reported clusters.

Surveys show that radiation levels from the VDT are seldom measurable above background with the exceptions of the extremely low frequency magnetic field and static electricity. Research on the biological effects of the magnetic field is equivocal and work is continuing. The results of animal work have not been positive at frequencies or levels of induced current density which pertain to VDTs.

The problem of stress is more difficult to assess. Some experienced clinicians believe that stress is detrimental to pregnancy. However, the nature of stress specific to VDT users, and how this may affect a pregnancy is, as yet, ill defined.

At present, it seems reasonable to conclude that a pregnancy may not be harmed by using a VDT and that statements to the contrary are not soundly based.

References

American Conference of Governmental Industrial Hygienists (1986) *Threshold Limit Values and Biological Exposure Indices for 1986–87* ACGIH, Cincinnati, USA.

American National Standards Institute (1982) *ANSI C95.1. Safety Levels with Respect to Human Exposure to Radiofrequency Electromagnetic Fields, 300 kHz to 100 GHz.* ANSI, New York, USA.

Axelsson, G. & Rylander, R. (1982) Exposure to anaesthetic gases and spontaneous abortion. response bias in a post questionnaire study. *Int J Epidemiol* **11**, 250-256.

Bergqvist, U. (1984*a*) Video display terminals and health. *Scand J Work Environ Health* **10 (Suppl. 2).**

Bergqvist, U. (1984*b*) Physical and chemical environments at VDT work stations—air ions, electrostatic fields, magnetic fields and PCBs. In *Allegations of Reproductive Hazards from VDUs.* Proceedings of an International Scientific Meeting, London, November 1984 (Pearce, B. G., ed.). Humane Technology, Nottingham, pp 55-65.

Bergqvist, U. (1986) The alleged reproductive hazard of VDU work—an overview In *Allegations of Reproductive Hazards from VDUs.* Proceedings of the Second International Scientific Meeting, London, November 1986, (Pearce, B. G., ed.), Humane Technology, Nottingham, pp. 3-14.

Binkin, N., Cates, W., Rochat, R. & Tyler, C. (1981) *Cluster of Spontaneous Abortions, Dallas, Texas.* Centre for Disease Control, Atlanta, Report no. EPI-80-113-2.

Butler, W. J. & Brix, K. A (1986) Video display terminal work and pregnancy outcome in Michigan clerical workers. In *Allegations of Reproductive Hazards from VDUs.* Proceedings of the Second International Scientific Meeting, London, November 1986, (Pearce, B. G., ed.) Humane Technology, Nottingham, pp. 67-92.

Cox, E. A. (1984) Radiation emissions from visual display units. In *Health Hazards of VDTs?* (Pearce, B. G , ed), John Wiley & Sons, Chichester, pp. 25-37

Delgardo, J., Leal, J., Monteagudo, J & Garcia, M. (1982) Embryological changes induced by weak, extremely low frequency electromagnetic fields. *J Anat* **134 (3),** 533-551

Denning, J. V. (1985) *Visual Display Units—Biomedical Aspects of Their Use.* London School of Hygiene and Tropical Medicine, London.

Doerfel, H. R., Graffunder, H & Piesch, E. (1986) Measurement of the effective dose equivalent due to low energy X-rays emitted from VDTs and colour television sets *Radiat Protect Dosimetry* **14** (2), 123-126.

Dubrov, A. P., Ostrjakov, J. A. & Turkov, V. D. (1968) Genetic effect of static electricity (in Russian) *Doklady Akademii Nauk SSSR* **178** (1), 216-217.

Ericson, A. & Kallen, B. (1986) An epidemiological study of work with video screens and pregnancy outcomes. *Am J Industr Med* **9,** 447-475.

Guy, A. (1984) *Health Hazard Assessment of Radio Frequency Electromagnetic Fields Emitted by Video Display Terminals.* Biomagnetics Research Laboratory, Centre for Bioengineering, University of Washington.

Health and Welfare, Canada (1983) *Investigations of Radiation Emissions from Video Display Terminals.* Report 83-EHD-91. Environmental Health Directorate, Ottawa.

Himmelberger, D. B , Brown, B. J & Cohen, E. N. (1978) Cigarette smoking during pregnancy and the occurrence of spontaneous abortion and congenital abnormality. *Am J Epidemiol* **108,** 470-479.

The Ionising Radiation Regulations (1985) Her Majesty's Stationery Office, London.

Juutilainen, J , Harri, M , Saali, K. & Lahtinen, T. (1986) Effects of 100 Hz magnetic fields with various waveforms on the development of chick embryos. *Radiat Environ Biophys* **25,** 65-74.

Kajiwara, S. (1984) *Work and Health in VDT Workplaces* (in Japanese). In-Service Training Institute for Safety and Health of Labour, Osaka, Japan, pp. 5-82

Knill-Jones, R. P. (1986) Epidemiological approaches to reproductive problems in the workplace. In *Allegations of Reproductive Hazards from VDUs.* Proceedings of the Second International Scientific Meeting, London, November 1986, (Pearce, B. G , ed.), Humane Technology, Nottingham, pp. 55-65.

Kurppa, K., Holmberg, P., Rantala, K., Nurminen, T. & Saxen, L. (1985) Birth defects and video display terminal exposure during pregnancy. *Scand J Work Environ Health* **11,** 353-356.

Labour Research Department (1985) Reproductive hazards. In *VDUs, Health and Jobs* LRD Publications Ltd, London, pp. 14-20.

Lee, W. E. (1985) Working with visual display units. *Br Med J* **291,** 989-991

Lee, B. V. & McNamee, R. (1984) Reproduction and work with visual display units. a pilot study. In *Allegations of Reproductive Hazards from VDUs.* Proceedings of an International Scientific Meeting, London, November 1984 (Pearce, B. G., ed.), Humane Technology, Nottingham, pp. 41-48.

Lewis, M. J , Esterman, A J. & Dorsch, M. M. (1982) A survey of the health consequences to females of operating visual display units. *Community Health Stud* **6 (2),** 130-134.

Mackay, C. (1987) The alleged reproductive hazards of VDUs. *Work and Stress* **1 (1),** 49-57.

Maffeo, S., Miller, M. & Carstensen, E. L. (1984) Lack of effect of weak low frequency electromagnetic fields on chick embryogenesis. *J Anat* **139,** 613-618

McDonald, A. D., Cherry, N., Delorme, C. & McDonald, J. C. (1986) Visual display units and pregnancy: evidence from the Montreal survey. *J Occup Med* **28,** 1226-1231.

McKinlay, A. F. (1986) The results of measurements of electromagnetic emissions from VDUs and a comparison with exposure standards. In *Allegations of Reproductive Hazards from VDUs.* Proceedings of the Second International Scientific Meeting, London, November 1986, (Pearce, B. G., ed.), Humane Technology, Nottingham, pp. 107-134.

Mikolajczyk, H., Indulski, J., Pawlazyk, M., Walicka, L. & Bienkowska-Januszko, E. (1986) Miscarriages in pregnant women employed at VDU and effects of TV radiation on experimental animals. In *Work with Visual Display Units.* Proceedings from the International Scientific Conference, Stockholm, May 1986.

Mild, K H. (1986) Biological effects of low frequency electromagnetic fields. In *Allegations of Reproductive Hazards from VDUs.* Second International Scientific Meeting, London, November 1986, (Pearce, B. G., ed.), Humane Technology, Nottingham, pp. 135-140

Murray, W. E. (1984) *Video Display Terminals: Radiation Issues.* IEEE CG&A pp. 41-44.

National Radiological Protection Board (1983) Revised guidance on acceptable limits of exposure during nuclear magnetic resonance imaging. *Br J Radiol* **56,** 974-977.

National Radiological Protection Board (1986) Advice on the protection of workers and members of the public from possible hazards of electric and magnetic fields with frequencies below 300 GHz: a consultative document. NRPB, Chiltern, UK.

National Radiological Protection Board (1987) Interim guidance on the implications of recent revisions of risk estimates and the ICRP 1987 Como Statement. NRPB-GS9. NRPB, Chiltern, UK.

Nilsen, A. (1982) Facial rash in VDU operators. *Contact Dermatitis* **8,** 25-28.

Olsen, W. C. (1981) Electric field enhanced aerosol exposure in VDU environments. Christian Michelsens Institute, Department of Science and Technology. 803604-1, NTIS, PB-82-159708.

Paulsson, L.-E., Kristiansson, I. & Malmstrom, I (1984) Radiation from VDUs. Document a84-08. National Institute for Radiation Protection, Sweden.

Purdam, J (1984) Adverse pregnancy outcome amongst VDU operators—the cluster phenomenon. In *Allegations of Reproductive Hazards from VDUs.* Proceedings of an International Scientific Meeting, London, November 1984 (Pearce, B. G., ed.), Humane Technology, Nottingham, pp. 27-40.

Roy, C. R., Joyner, K. H , Gies, H. P , Bangay, M. J. & Cornelius, W. A. (1983) Measurement of electromagnetic radiation emitted from visual display terminals. Report of the Australian Radiation Laboratory No. ARL/TR053, Yallambie, Australia

Repacholi, M. (1985) Video display terminals—should operators be concerned? *Australasian Physical and Engineering Sciences in Medicine* **8 (2),** 51-61.

Saunders, R. & Smith, H. (1984) Safety aspects of NMR clinical imaging. *Br Med Bull* **40,** 148-154

Sandstrom, M. (1986) *Effects of Weak Pulsed Magnetic Fields on Chick Embryogenesis.* Department of Zoophysiology, University of Umea, Sweden.

Tribukait, B., Cekan, E. & Paulsson, L.-E. (1986) Effects of pulsed magnetic fields on embryonic development in mice. Department of Radiobiology, Karolina Institute, Stockholm.

Ubeda, A., Leal, J., Trillo, M., Jimenz, M. & Delgardo, J. (1983) Pulse shape of magnetic fields influences chick embryogenesis. *J Anat* **37 (3),** 513-536.

Villforth, J. C. (1981) *An Evaluation of Radiation Emission from Video Display Terminals.* Bureau of Radiological Health, HHS Publication FDA 81-8153, Rockville, USA.

Westerholm, P. & Ericson, A. (1986) Pregnancy outcome and VDT work in a cohort of insurance clerks. In *Work With Display Units.* Proceedings of an International Scientific Conference, Stockholm, pp. 665-668

World Health Organization (1981) *Environmental Health Criteria Document 16: Radiofrequency and Microwaves.* WHO, Geneva.

World Health Organization (1984) *Environmental Health Criteria Document 35· Extremely Low Frequency Fields.* WHO, Geneva

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Medical malpractice claims in obstetrics and gynaecology: comparisons between the United States and Britain

LOIS QUAM, ROBERT DINGWALL, PAUL FENN

Summary. Obstetricians and gynaecologists have been particularly affected by the increase in the cost and number of medical malpractice claims in Britain. US obstetricians and gynaecologists have experienced a disproportionately higher rate of claim than other practitioners in that country. This article reviews the US experience of obstetrics and gynaecology malpractice claims and questions the validity of showing comparisons between the US and the UK. However, even if British malpractice claims do not reach the level of American claims, the effects of claims on the National Health Service, recruitment to obstetrics and gynaecology, and clinical practice are significant.

The increasing number and cost of medical negligence claims in the UK has aroused fears that the American medical malpractice crisis may be reaching these shores (Symonds 1985; Smith 1986). The validity of such fears depends upon an accurate analysis of the US situation. It has been argued elsewhere that the institutional differences between the two countries make a simple replication unlikely, unless there are further moves towards privatizing both the costs of health care provision and of remedying its failures (Quam *et al.* 1987*a*, *b*). Nevertheless, obstetrics and gynaecology do appear to be in a particularly exposed position and even a relatively small shift in the pattern of legal claims could have significant implications for NHS resources, recruitment to the speciality and everyday clinical practice.

The Frequency and Severity of Obstetrics and Gynaecology Claims in the USA

American obstetricians and gynaecologists experience a rate of claims which is second only to that of neurosurgeons (St Paul Fire and Marine Insurance Co. 1986). While obstetricians and gynaecologists accounted for 5·2% of all US physicians in 1984, they constituted 12·4% of all physicians involved in malpractice claims; 10·0% of all claims paid and 26·9% of total indemnity payments (US General Accounting Office (GAO) 1987). Moreover, general practitioners who practised any obstetrics had a significantly higher frequency of claims than those who did not (St Paul Fire and Marine Insurance Co. 1986).

Claims against obstetricians and gynaecologists are on the increase. The St Paul Company, the largest medical liability insurer in the USA, reported a frequency rate of 43·7 claims per 100 insured obstetricians and gynaecologists in 1985, an increase of 59% over 1981.

Gynaecologists appear to have a higher rate of claims than obstetricians. A survey by the American College of Obstetricians and Gynaecologists (ACOG 1983) found that 41·3% of claims reported by their members were for gynaecological surgery. A repeat of the survey in 1985 produced similar results (ACOG 1985). Further support is provided by the study of open and closed claims conducted by the Risk Management Foundation of the Harvard Medical Institutions. They identified 66 relevant

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Centre for Socio-Legal Studies, Wolfson College, Oxford OX2 6UD
LOIS QUAM *Research Assistant*
ROBERT DINGWALL *Research Fellow*
PAUL FENN *Research Fellow*

Correspondence: Dr Robert Dingwall

claims between April 1976 and September 1983. Of these, 57% were associated with gynaecological treatment and 43% with obstetrics (Risk Management Foundation 1986*a*).

Obstetricians, however, tend to have more severe claims, by which the insurance industry means a higher average cost of settlements. The US General Accounting Office reported that in 1984 obstetrics claims had the highest median and average indemnity payments of all medical liability claims. The median claim in obstetrics for 1984 was $65 000 (£40 625) (US GAO 1987). The St Paul Company (1986) reported an average expenditure of $91 350 (£62 145) per claim in 1984 and 1985, including their own legal costs.

But this is distorted by the high risk of claims relating to newborn infants. Injuries to mothers are much more common but relatively inexpensive to settle. The Harvard Risk Management Study found that injuries to newborns represented 33% of claims but 76% of the amount paid in settlements; 86% of these claims related to neurological defects including cerebral palsy (Risk Management Foundation 1986*a*).

Medical Malpractice Insurance in the USA

Medical malpractice insurance premiums are affected by two sets of factors: those which are general to the business and those which reflect the special circumstances of each area of practice (O'Leary & Kahan 1984).

All insurance involves the collection of money in the present to meet liabilities in the future. But that money can be invested between receipt and payment and the interest earned on it also contributes to the resources of the insurer facing claims or paying dividends to shareholders. Insurers can also reinsure against the risk of having to pay out on the policies they have written. Medical malpractice insurance has always been a difficult line of business because of the lengthy time-lags between an injury and the filing of a claim. Fifteen per cent of US claims stretch over 4 years (US General Accounting Office 1986*a*). This is a particular problem for obstetrics since in most states the insurers' liability does not cease until the child's right to file a claim at the age of majority has lapsed (US Attorney General 1986). These time-lags complicate premium rate setting. If insurers fail to estimate their liability correctly, and set premiums and investment targets accordingly, they can be placed under great stress when the claims actually have to be settled. This has been a particular problem in recent years when the profitability of insurers' investments has declined (Koehn 1986; Somers 1977) and reinsurance through the City of London has become more difficult to obtain (US General Accounting Office 1986*b*). These factors have contributed to a general rise in medical liability premiums (US Attorney General 1986).

Premiums are further influenced by the severity and frequency of claims against practitioners in each specialty. The experience of insurers with obstetrics and gynaecology has led to a rating second only to that of neurosurgery and a more rapid rate of increase than any other risk group. The average premium paid by specialists in obstetrics and gynaecology rose from $10 900 in 1982 to $18 800 in 1984, an increase of approximately 72% (US General Accounting Office 1986*b*). But there are wide variations between and within states, reflecting local claims experience. Two New England states, Maryland and Maine, provide an example. As of 1 July 1985, an obstetrician/gynaecologist in Maryland paid an average annual premium of $42 434 (£22 630) while his or her counterpart in Maine paid £12 928 (£8 750) for the same policy. There are equally wide differences within populous states like New York and Pennsylvania. Long Island obstetricians and gynaecologists paid premiums 14 to 121% higher than obstetricians and gynaecologists practising in the other three New York rating areas (US General Accounting Office 1986*b*).

It must be recognized, though, that these premium rates still represent only a relatively small proportion of the average American obstetrician's or gynaecologist's gross income. In 1985 average premiums amounted to 8% of an average gross income of $235 000 (£160 000) (US General Accounting Office 1986*b*) Like other doctors, these specialists have been able to maintain their real incomes by a combination of increased fees and favourable tax treatment (ACOG 1985) Most US practitioners have experienced real income increases in the 1980s (Owen 1985) In those states where obstetricians' and gynaecologists' net incomes have declined, malpractice premiums are merely one among a number of factors involved. Others, including demographic change, local oversupplies of specialists and the shift from fee for service to prospective payment systems (Anon

Table 1. Physician average premiums and per cent increase from 1982 to 1984 by specialty

Specialty	Physician premium ($) 1982	1983	1984	Per cent increase
All physicians	5800	7100	8400	45
General/family practice	3500	4400	4600	31
Internal medicine	3700	4400	4900	32
Surgery	9900	10 900	13 400	35
Paediatrics	2900	3900	3500	21
Obstetrics/gynaecology	10 900	14 100	18 800	72

Source: US General Accounting Office (1986*b*)

Table 2. Physician average premiums as percentages of average gross income for 1982 and 1984 by specialty

	1982		1984	
Specialty	Premiums ($)	%	Premiums ($)	%
Paediatrics	2900	2	3500	2
General practice	3500	2	4600	3
Internal medicine	3700	2	4900	2
Surgery	9900	4	13 400	5
Obstetrics/gynaecology	10 900	5	18 800	8

Source: US General Accounting Office (1986*b*).

1986), which have restricted the scope for passing on cost increases in higher charges, seem much more powerful influences (Ginzberg 1986).

The main problem with malpractice insurance is one of availability rather than cost. After a collapse in the mid 1970s the supply stabilized thanks to significant state subsidies to private insurers and the creation of new physician-owned mutual funds to write insurance for their members (Danzon 1985). But insurance availability has recently become a problem again since the largest private insurer, the St Paul Company, has placed a moratorium on new policies (St Paul Fire and Marine Insurance Co. 1986) and the physician-owned mutuals are having to pay out after their initial financial honeymoon because of the long time-lags from incident to settlement of claims (Mixson 1986).

The Prospects for a Medical Malpractice Crisis in Britain

The institutional differences between Britain and the USA play an important part in explaining the variation in their experience of malpractice claims. High rates of claiming and litigation are likely to be intrinsic features of American-style systems of welfare, health and legal service provision. In a private system, the costs of errors are privately borne. Where the provision of these services is collectivized, pressures to litigate are greatly reduced, and the possible cost of awards is diminished. To the extent that the UK moves away from public provision of health care and income support, an increasing propensity to claim larger sums must be expected.

The National Health Service (NHS) is a particularly important restraint on obstetrics litigation in Britain. In the US the lack of free medical and social care for handicapped infants means that their parents face extremely high costs (Shearer 1986; Sandberg 1984). Since public support is not available and private insurers are reluctant to provide cover, parents seek compensation through litigation. As the editor of the *Obstetrical and Gynecological Survey* (1986) wrote: 'As the evidence collects that the obstetrician should not be blamed for cases of cerebral palsy, one wonders why attorneys advertise in newspapers soliciting parents of cerebral palsy victims for appointments so that the case can be investigated. One possible contributing factor is that parents of a child with cerebral palsy have a huge burden to bear by themselves. Most states and communities have no system to help the families deal with the expense and extra care these children need. Since public assistance in this country is not available to help share the load as in most other industrialized countries, the parents seek help through legal means and it is the professional liability companies to whom they turn.'

English judges are not insensitive to this. In the case of Whitehouse *v.* Jordan (1980) Lord Justice Lawton referred to the 'sorrow' with which he rejected the claim of negligence against an obstetrician. But he also emphasized that the case of handicapped babies was better dealt with by the whole community than the chance results of trying to establish a private fault through legal action (Whitehouse *v.* Jordan 1980).

The NHS reduces the need for litigation by ensuring access to medical care throughout life. Litigation in the US is fuelled by the sheer cost of extra care following an iatrogenic injury or treatment (Liston & Siegel 1985). In addition to the immediate expense, a patient with a permanent disability may face continuing difficulty in obtaining insurance coverage or have to pay excess premiums. But the restraint to litigation represented by the NHS is vulnerable unless the level of resources is adequate to ensure reasonable treatment, so that there is no need to purchase care, and as long as the standards of professional discipline encourage confidence in the medical staff. Where funding is insufficient, producing stress and fatigue among doctors, injuries and iatrogenic communication breakdowns also seem likely to increase (Green & Taylor 1984).

The situation is also influenced by the nature of the legal process in the two countries. While large areas of the US and UK share a common legal tradition, there are important differences in the access of claimants to the courts, in their ability to assemble a worthwhile case, and in the response they are likely to meet. Access to the legal services in the US is facilitated by the greater number of practising lawyers: twice as many per million population as in the UK (Galanter 1983). Moreover, US patients retain a legal right to their medical records and can more easily obtain other relevant medical documents in discovery prior to trial. This difference in access to medical evidence is significant for obtaining legal assistance, assembling and preparing a case (Capstick 1986; Teff 1985; Napley 1977).

American statutes and court decisions have generally left US plaintiffs in a more favourable position than their counterparts in the UK. In particular, US juries are notably more willing to uphold claims arising from failures or delays in diagnosis (Brenner & Jessesse 1983). Claims of this type represented the single largest group of claims against gynaecologists in the Harvard Study (Risk Management Foundation 1986*b*). In the UK, such claims are unlikely to be successful except in cases alleging gross negligence, such as the failure to notify a patient of a positive cervical smear.

Despite these various restraints, there is some evidence of an increase in claims in Britain, particularly in obstetrics and gynaecology (Medical Defence Union 1986; Medical Protection Society (MPS) 1986). There are three major types of claims in British obstetrics: anaesthetic mishaps, failure to observe fetal stress early enough, and the improper performance of instrumental or caesarean deliveries (Capstick 1986). For gynaecologists, an increase in claims alleging failed sterilization has been reported (Symonds 1985; MDU 1986; MPS 1986). These are essentially the same types of event which give rise to claims in the US (Risk Management Foundation 1986*b*).

The English defence societies tend not to publish their figures in a consistent fashion. However, some indication of the trends can be obtained from the smaller sample of doctors insured by the Medical and Dental Defence Union of Scotland (MDDUS). These show an increase in obstetrics and gynaecology claims as a proportion of total claims. One third of obstetrics/gynaecology claims from 1982 to 1985 for MDDUS members related to labour and delivery. Of those cases 56% alleged improper performance of delivery resulting in neurological damage or death to the infant. Laparoscopies, most frequently in connection with allegations of failed sterilization, accounted for one quarter of all claims Other procedures with multiple claims were hysterectomy, problems involving the intrauterine contraceptive device, the termination of pregnancy, failed tubal ligation, improper management of antenatal care and faulty prenatal diagnosis (MDDUS 1985).

These considerations should not encourage loose talk of a British 'malpractice crisis'. But a relatively small increase in claims against obstetricians and gynaecologists, or other practitioners, could have a significant effect on British health care. Unless accommodated by increased funding, a rise in claims would increase pressure on NHS resources. It may also affect recruitment to high-risk specialties, like obstetrics and gynaecology, and influence clinical practice.

The Implications of an Increase in British Litigation Rates

Health authorities, as public bodies, do not insure against tort liability claims and must meet the legal costs of claims and any compensation, agreed or awarded, out of their general budget. The direct impact on NHS resources available for patient care may be severe (Klcss 1984). While damage payments by health authorities are likely to fluctuate radically from year to year, an authority's budget cannot be adjusted in the short run, in relation to the cost of litigation. In a year with a particularly large settlement or a large number of settlements, it may mean the temporary closure of a ward or a delay of planned capital expenditure (Symonds 1985).

The increasing frequency and severity of medical malpractice claims in obstetrics and gynaecology, relative to other specialties, may have a deleterious effect on recruitment to the specialty (Symonds 1985), although the factors influencing specialty choice in medical care are not well understood and further research is needed on this point. At present, such recruitment effects are mitigated by the medical defence societies' uniform charge Should insurance companies offer medical liability policies with differential rates for high- and low-risk specialties, the effect on recruitment to obstetrics and gynaecology may be substantial. In the US, the effect of vastly different insurance premiums by specialty has not been severe because specialties with higher premiums (St Paul Fire and Marine Insurance Co. 1986) are also those with higher incomes (Owen 1985). American obstetricians and gynaecologists can raise their fees to meet premium costs. British obstetricians and gynaecologists cannot. As a consequence, such differential rates, despite tax deductions available, would significantly distort recruitment to specialties unless NHS salaries were adjusted accordingly. Even if extra allowances were paid, of course, potential recruits might also be deterred by non-economic considerations like the stress of frequent claims and possible court appearances.

In theory, the tort system induces physicians to practise more carefully by penalizing them financially for negligent behaviour (Reder 1976) The courts, in awarding damages to patients, give doctors a financial incentive to prevent injuries. In practice, however, this signal may be distorted if the court errs in finding negligence or setting damages (Schwartz & Komesar 1978). Amongst the American and British medical professions, it is widely held that these distortions are so significant that clinical practice is adversely affected. The effect is usually called defensive medicine, defined as a deviation from sound practice induced by a threat of liability (Hershey 1972).

In obstetrics, it has been argued that the rate of caesarean section is, in part, a response to a growing number of claims alleging the negligent management of labours resulting in neurological injuries to infants (Chalmers 1985; Macfarlane & Mugford 1986). Doctors are encouraged to intervene in order to deflect blame for defects in the infant and provide a defence against medical litigation (Klein 1984). More than 10 years ago, O'Driscoll *et al.* (1975) identified 'a subtle influence in obstetrics that operates to absolve a doctor who intervenes in the case of a normal pregnancy and which by implication exposes a colleague to censure when an infant is born dead'. This incentive may be strengthened by the fact that litigation is almost never attached to unnecessary interventions (Sandberg 1984) even though the risk of maternal morbidity is increased (Oki 1986).

It is difficult to isolate the effect of the threat of legal action on caesarean sections, or medical practice generally, because clinical decision making is influenced by many factors, including the payment system, training, work environment, peer esteem, and the physical stress or fatigue of the doctor. The BMA's Working Party on No-Fault Compensation confronted this problem when they attempted to quantify the cost of 'defensive medicine' practised in the UK. They concluded they were unable to do so because the number of variables affecting clinical practice inhibited estimation of any significant causal relation between litigation threats and changes in clinical practice (BMA 1983) Indeed, with fixed and uniform defence society subscription rates, it is hard to identify just what financial penalty could be attributed to litigation in Britain.

Rising caesarean section rates have been a feature of obstetric care in many countries in

Table 3. Obstetric and gynaecology claims in relation to MDDUS claim experience 1982–1984

	1982	1983	1984
Total claims	205	305	307
OB/GYN claims (*n*)	35	85	95
as percentage of total	17%	28%	31%

Source· MDDUS (1985)

Table 4. Caesarean section rates (%)* for selected countries 1970–1983

Year	United States	Canada	Sweden	Scotland	Denmark	England and Wales	Norway	Netherlands
1970	5·5	6·0			4·1	4·3	2·2	2·1
1971	5·8	6·4			4·3	4·6	2·4	2·0
1972	7·0	7·2			4·6	4·9	2·5	2·2
1973	8·0	8·0	5·5		5·0	5·0	3·0	2·5
1974	9·2	9·0	6·8		6·0	5·3	3·6	2·7
1975	10·4	9·6	7·8	8·1	6·4	5·7	4·0	2·8
1976	12·1	10·8	9·6	9·3	7·1	6·3	5·0	2·9
1977	13·7	12·1	10·9	10·0	8·0	7·1	6·4	3·5
1978	15·2	13·7	11·0	10·7	9·2	7·3	7·3	3·9
1979	16·4	15·1	11·6	11·1	10·3	8·2	8·0	4·3
1980	16·5	16·1	12·0	11·5	10·5	8·8	8·3	4·7
1981	17·9		12·3	18·8		9·1	8·7	4·9
1982			12·5	12·5		10·1	9·0	5·4
1983	20·3					10·1	9·4	
1984						10·2		

* These data come from several sources, so some refer to the percentage of women delivered by caesarean section and others to the percentage of babies born by caesarean section
Source: Macfarlane & Mugford (1986).

spite of wide variation in litigation rates (Notzon *et al.* 1987). These can be equally well explained by changing clinical indications, policies on repeat caesarean section, saving clinician's time, and in the US, greater financial reimbursement for caesarean sections (Taffel & Placek 1983; NICHHD 1981; Marieskind 1979). The increase in the British caesarean section rate has been ascribed to a multiplicity of factors, particularly the tendency towards repeat section (Yudkin & Redman 1986). In the US repeat sections account for roughly 30% of the increase in the caesarean section rate in the past decade (Phelan 1986). While the Maternity Alliance surveys in 1983 and 1986 (Maternity Alliance 1983, 1986) reported that the threat of litigation was cited as the second most common reason for performing caesarean sections, the well-recognized potential biases in such self-reported responses to surveys which attempt to measure motivation require a cautious approach to the validity of these findings (Danzon 1985).

Concern over litigation may also have positive benefits for patients (Medical Protection Society 1986). For example, the ACOG (1985) survey reported that 58·8% of obstetricians and gynaecologists responding said that they were now monitoring patients more closely and 44·2% said they consulted other doctors more frequently because of this. The American Medical Association (AMA) 1983 survey of 1240 doctors reported 57% of respondents claiming that they kept better records (AMA 1984). Changes in clinical practice resulting from the threat of litigation should not necessarily be assumed invariably to act against the patient's interests.

The Case for Reform

It is premature to talk of an American-style medical malpractice crisis in obstetrics and gynaecology in Britain. However, the high potential awards in claims alleging neurological damage in infants and the increasing frequency of claims against obstetricians and gynaecologists give cause for serious and proper concern. The precise implications are difficult to establish without proven published data on obstetrics and gynaecology claims in Britain. Such data are held in the files of health authorities and defence societies but have yet to be made available on any scale for analysis. It should worry both clinicians and patients that practitioners may alter their clinical practice in response to what they perceive as increasing risks of litigation when their information is so poor. Anecdotes and professional gossip are inadequate methods for adapting clinical behaviour to reduce claims. What is urgently needed is a comprehensive study of obstetrics and gynaecology claims, on the model of that conducted at Harvard (Risk Management Foundation 1986*a, b*) which would pinpoint allegations, characteristics and costs of claims and provide a basis for public policy reform. It is notable that, despite the competitive nature of the health care and insurance industries in the US, commercial confidence is much less of an inhibition on the free release of information than the secretive tradition of British public institutions.

There have been recent expressions of support (Symonds 1985; Brudenell 1985) among obstetricians and gynaecologists, and the profession in general (Smith 1986; Brahams 1985) for replacing the tort system with a no-fault scheme along the lines of those operating in Sweden and New Zealand. Tort litigation is an inefficient means of compensating victims of personal injury (Harris *et al.* 1984): the costs of establishing negligence regularly exceed the sums paid in compensation (Lord Chancellor 1986). Nevertheless, it has a well-established place in the overall pattern of compensation to victims and incentives to high quality provision of care in Britain. This contribution is poorly understood at present but proper research and analysis would be needed to help policymakers develop effective alternatives if tort were to be abandoned. On its own a no-fault system may neither deter negligence nor give early warning of avoidable adverse events, like many of the failed sterilization cases.

Alternative methods of compensating patients must take into account the deterrence objective of the system, its aspiration to discourage harmful practice (Schwartz & Komesar 1978). Proper research and analysis of medical negligence claims, which could help policymakers develop an effective alternative to the tort system, is sorely lacking. Obstetricians, gynaecologists and their patients have much to gain by pressing for better information.

References

Anon. (1986) Mass. Obstetricians pinched by rate hikes, income restrictions. *ACOG Newsletter* **30, 1,** 7.

American College of Obstetrics and Gynecology (1983) *Professional Liability and its Effects. Report of a Survey of ACOG's Membership* ACOG, Washington, DC

American College of Obstetrics and Gynecology (1985) *Professional Liability Insurance and its Effects Report of a Survey of ACOG's Membership.* ACOG, Washington, DC

American Medical Association Special Task Force on Professional Liability (1984) *Professional Liability in the 1980s.* AMA, Chicago.

Brahams, D. (1985) 'No fault' compensation: reform of present system long overdue *Lancet* **ii,** 1403-1404.

Brenner, L. H. & Jessesse, W. F. (1983) Delays in diagnosis: a problem for quality assurance. *QRB* **Nov.** 337-344.

British Medical Association (1983) *Report of the No-Fault Compensation for Medical Injury Working Party.* BMA, London

Brudenell, M (1985) Litigation in obstetrics and gynaecology (letter). *Br J Obstet Gynaecol* **92,** 1072-1073.

Capstick, B. (1986) *Law in the Health Service Patient Complaints and Litigation.* National Association of Health Authorities, Birmingham.

Chalmers, I (1985) Trends and variations in the use of caesarean delivery. In *Perinatal Medicine: Proceedings of the IX European Congress of Perinatal Medicine* (Clinch, J., ed.), MTP Press, Lancaster, pp. 145-149.

Danzon, P M. (1985) *Medical Malpractice: Theory, Evidence and Public Policy.* Harvard University Press, Cambridge, MA.

Galanter, M. (1983) Mega-lawyers and mega-lawyering in the contemporary United States In *The Sociology of the Professions. Lawyers, Doctors and Others* (Dingwall, R. & Lewis, P. S. C., eds), Macmillan, London.

Ginzberg, E. (1986) Sounding board: the destabilization of health care. *N Engl J Med* **315,** 757-760.

Green, R. A. & Taylor, T. H. (1984) An analysis of anesthesia medical liability claims in the United Kingdom 1977–1982. *Int Anesthesiol Clin* **22,** 73-89

Harris, D., Maclean, M., Genn, H., Lloyd-Bostock, S., Fenn, P., Corfield, P. & Brittan, Y. (1984)

Compensation and Support for Illness and Injury. Clarendon Press, Oxford.

Hershey, N. (1972) The defensive practice of medicine: myth or reality. *Milbank Mem Fund Q* **19**, 939-986.

Klein, L. (1984) Cesarean birth and trial of labour. *Female Patient* **9**, 106-117.

Kloss, D. (1984) The duty of care. *Br Med J* **289**, 66-68.

Koehn, S. B. (1986) Hospital corporate liability: an effective solution in controlling private physician incompetence? *Rutgers Law Rev* **32**, 342-388.

Liston, S. L & Siegel, L. G. (1985) Another cause for litigation (letter) *JAMA* **253**, 3095.

Lord Chancellor's Department (1986) *Civil Justice Review: Personal Injuries Litigation.* Lord Chancellor's Department, London.

Macfarlane, A. & Mugford, M. (1986) An epidemic of caesareans? *J Matern Child Health* **11**, 38-42.

Marieskind, H. I (1979) *An Evaluation of Cesarian section in the United States.* DHEW, Washington, DC.

Maternity Alliance (1983) *One Birth in Nine. Caesarean Section Trends since 1978.* Maternity Alliance, London.

Maternity Alliance (1986) *An Epidemic of Caesareans?* Maternity Alliance, London.

Medical and Dental Defence Union of Scotland (1985) *Annual Report 1984.* MDDUS, Glasgow.

Medical Defence Union (1986) *Annual Report 1985* MDU, London.

Medical Protection Society (1986) *Annual Report 1985.* MPS, London.

Mixson, W. T. (1986) The spring of hope. *Obstet Gynecol* **67**, 153-156.

Napley, D. (1977) The lawyer as representative of the patient. In *The Influence of Litigation on Medical Practice* (Wood, C., ed.), Academic Press, London.

National Institute of Child Health and Human Development (1981) *Cesarean Childbirth: Report of a Consensus Development Conference* NICHHD, Bethesda, MD.

Notzon, F. C., Placek, P. J. & Taffel, S. M. (1987) Comparisons of national cesarean rates. *N Engl J Med* **316**, 386-389.

O'Driscoll, K., Carroll, C. J. & Coughlan, M (1975) Selective induction of labour *Br Med J,* **iv**, 727-729.

O'Leary, J. F. & Kahan, R. (1984) Medical liability insurance: crisis revisited. *Int Anesthesiol Clin* **22**, 117-131.

Oki, E. Y. (1986) External cephalic version. *West J Med* **144**, 68-69.

Owen, A. (1985) Doctors' earnings: the year of the big surplus. *Med Economics* **9 Sept.**, 195-215.

Phelan, J. P. (1986) Vaginal delivery after previous cesarian section. *West J Med* **144**, 68-70

Quam, L., Dingwall, R & Fenn, P. (1987*a*) Medical malpractice in perspective. I. The American experience. *Br Med J* **294**, 1529-1532.

Quam, L., Fenn, P. & Dingwall, R. (1987*b*) Medical malpractice in perspective. II The implications for Britain. *Br Med J* **294**, 1597-1600.

Reder, M. W. (1976) Medical malpractice: an economist's view. *Am Bar Foundation Res J* **1976**, 511-563

Risk Management Foundation of the Harvard Medical Institutions (1986*a*) Fetal monitoring problems during labour associated with most serious OB claims. *FORUM* **7**, **2**, 19-20.

Risk Management Foundation of the Harvard Medical Institutions (1986*b*) Diagnostic errors most frequent and costly allegations in GYN claims. *FORUM* **7**, **2**, 17-18.

St Paul Fire and Marine Insurance Company (1986) *Physicians and Surgeon Update. An Annual Report from the St Paul Co.* St Paul Co., St Paul, MN.

Sandberg, E C (1984) Round table discussion: cesarean section. *Am J Obstet Gynecol* **149**, 41-43.

Schwartz, W. A. & Komesar, N. K. (1978) Doctors, damages and deterrence: an economic view of medical malpractice. *N Engl J Med* **298**, 1282-1289

Shearer, M H (1986) When perinatal caregivers enter the insurance business. *Birth* **13**, 151-152.

Smith, R (1986) When things go wrong. *Br Med J* **293**, 461-462.

Somers, H. M. (1977) The malpractice controversy and the quality of patient care. *Milbank Mem Fund Q* **55**, 193-232.

Symonds, E. M (1985) Litigation in obstetrics and gynaecology. *Br J Obstet Gynaecol* **92**, 433-436.

Taffel, S. M. & Placek, P. J. (1983) Complications in cesarian deliveries: United States 1980. *Am J Public Health* **73**, 856-860

Teff, H. (1985) Consent to medical procedures: paternalism, self-determination or therapeutic alliance? *Law Q Rev* **101**, 432-453

US Attorney General's Tort Policy Working Group (1986) *The Causes, Extent and Policy Implications of the Current Crisis in Insurance Availability.* Government Printing Office, Washington, DC

US General Accounting Office (1986*a*) *No Agreement on Problems or Solutions.* GAO, Washington, DC.

US General Accounting Office (1986*b*) *Medical Malpractice Costs Increased but Varied Among Physicians and Hospitals* GAO, Washington, DC

US General Accounting Office (1987) *Characteristics of Claims Closed in 1984.* GAO, Washington, DC.

Whitehouse *v.* Jordan (1980) 1 All ER 650, 659.

Yudkin, P. L. & Redman, K W G. (1986) Caesarean section dissected 1978–1983. *Br J Obstet Gynaecol* **93**, 135-144.

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Endocrine effects of 17 alpha-hydroxyprogesterone caproate during early pregnancy: a double-blind clinical trial

FRANS J. L. REIJNDERS, CHRIS M. G. THOMAS, WIM H. DOESBURG, RUNE ROLLAND, TOM K. A. B. ESKES

Summary. The clinical and endocrine effects of progestogen therapy in early pregnancy were investigated using a double-blind randomized trial in 64 patients who had a viable fetus at 6 weeks gestation and had an increased risk of miscarriage. The patients were randomly allocated to receive either 17 alpha-hydroxyprogesterone caproate or a placebo between 7 and 12 weeks gestation. Four fetal ultrasonographic variables and 17 maternal endocrine variables were studied in each woman. Only four maternal serum variables (17 alpha-hydroxyprogesterone, prolactin, thyroxin and thyroxin binding globulin) rose significantly. The serum progesterone levels in the hormone supplemented group were on average 20% higher than in the placebo group but the difference was not statistically significant. However, the relation between the progesterone levels and the fetal outcome was not clear. Therefore it is not advisable to prescribe 17-OHP-C during early pregnancy to prevent a miscarriage.

About 15% of all clinically recognized pregnancies end in miscarriage (Stirrat 1983), but when pregnancy is detected with very sensitive hormonal assays it appears that almost 60% will end in miscarriage before 11 completed weeks gestation (Edmonds *et al.* 1982). However, after a viable fetus has been detected with ultrasound in the 10th week of an uncomplicated pregnancy the reported fetal loss is only 2–6% (Christiaens & Stoutenbeek 1984; Gustavii 1984; Gilmore & McNay 1985; McFadyen 1985) and in threatened miscarriage with a viable fetus only 3–13% will end in miscarriage (Anderson 1980; Mantoni 1985).

In almost 60%, the cause of fetal loss is related to chromosomal disorders of the conceptus (Lauritsen 1976). For most of the others, the causes are unknown, but some may be related to endocrine disorders. Laboratory studies have suggested that progesterone plays an important role in the maintenance of pregnancy (Csapo & Pulkkinen 1978), but clinical studies have not shown any beneficial effects of progestogens in early pregnancy (Shearman & Garrett 1963; Goldzieher 1964; Tognoni *et al.* 1980), perhaps because of the limited role of hormonal dis-

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Catholic University, Nijmegen, The Netherlands
Institute of Obstetrics and Gynaecology
CHRIS M. G. THOMAS
RUNE ROLLAND
TOM K. A B. ESKES

Department of Statistical Consultation
WIM H. DOESBURG

Department of Obstetrics and Gynaecology, St Joseph Hospital, Eindhoven, The Netherlands
FRANS J. L. REIJNDERS

Correspondence: Dr F. J. L. Reijnders, Department of Obstetrics and Gynaecology, Stichting Doetinchemse Ziekenhuizen, PO Box 169, 7000 AD Doetinchem, The Netherlands

orders in the aetiology of early miscarriage. Furthermore, there is no reliable method for selecting patients who might benefit from hormonal treatment. Some obstetricians prescribe progestogens for patients with suspected corpus luteum insufficiency or a history of recurrent miscarriage. Up to 28% of the market share of progestogens was used for the indication 'threatened abortion' (Tognoni *et al.* 1980). There are at present no known teratogenic effects of 17 α-hydroxyprogesterone caproate (17-OHP-C) (Michaelis *et al.* 1983; Katz *et al.* 1985). In spite of the wide use of progestogens during pregnancy (Michaelis *et al.* 1983; Katz *et al.* 1985), there is hardly any information about the endocrine effects of these hormones when taken during the first trimester. This information could lead to a more rational basis for prescribing hormonal agents in selected patients. Therefore we performed a double-blind randomized controlled clinical trial in patients at increased risk of miscarriage in an attempt to describe endocrine changes of several variables known to be involved in the maintenance of pregnancy.

In statistical terms the study was designed to test the null hypothesis that for each of the hormonal variables examined the distribution of the serum hormone concentration was the same in the placebo and the 17-OHP-C treated groups at any time during the treatment period. A second hypothesis tested was that in the 4-week period after hormone administration, the distribution of the change in serum hormone concentration was the same in the placebo and the 17-OHP-C treated groups.

Patients and methods

Study design

It was decided to concentrate in this study on changes in hormone levels due to the administration of 17-OHP-C. Suppose, for a certain hormonal variable—measured once in an individual patient during a given week of pregnancy—the coefficient of variation (SD/mean×100%) is about 50% (as is the case for most of the variables studied) and 17-OHP-C treatment changes the serum concentration by 30%. Then, with a probability of 80% the comparison of the two sample-distributions will reveal a significant difference (*t*-test on the logarithm of the serum concentration) when there are 40 patients in each study group. So it was decided for reasons of management, based on an entry of 40 patients per year, to enrol patients into the study for a period of 2 years. During this period 69 patients were selected according to one or more of the following selection criteria: pregnancy after ovulation induction, two or more previous miscarriages (proven by histological examination or a positive pregnancy test), or a period of infertility of more than 12 months. Of these 69 patients, only 64 with a viable fetus at 6 weeks (after ultrasound detection) were admitted to the study. All patients gave their informed consent. A total of 80 coded ampoules (40 containing placebo and 40 17-OHP-C) were ordered randomly and administered to the patients according to their sequence of entry The ampoules were coded by Schering AG and the code was held by the statistical department which also controlled the allocation procedure. At weekly intervals between 7 and 12 weeks gestation (menstrual age) the patients received 500 mg of 17-OHP-C in 2 ml oil (Proluton-Depot, Schering AG, West Berlin) or a placebo (2 ml oil) injected intramuscularly. All patients were seen weekly between 7 and 12 weeks gestation and again at 14 and 16 weeks gestation. At each visit, blood was obtained from the cubital vein between 13.30 and 18.00 hours and the serum stored at −70 °C. At each visit during the study period the patients had their pregnancy checked by ultrasound (Real Time Linear Array Scanner, SAL-20A, Toshiba Co., Tokyo, Japan).

Hormone assays

It can be expected that 17-OHP-C will cause changes in serum levels of 17α-hydroxyprogesterone (17-OHP), progesterone, and oestradiol (E2) and also in prolactin (PRL), human chorionic gonadotrophin (hCG) and thyroid hormones. These were all measured by radioimmunoassay (RIA) or immunoenzymetric assay (IEMA) as described by Dony *et al.* (1985), Thomas *et al.* (1977) and van Geelen *et al.* (1981) for 17-OHP, E2 and progesterone and PRL respectively. hCG was determined using a Tandem-E hCG Immuno-Enzymetric Assay-kit, Hybritech, Europe SA, Liege, Belgium. Serum levels of thyroxine (T4), free thyroxine (FT4), triiodothyronine (T3) and thyroid binding globulin (TBG) were determined with RIA-kit donated by Clinical Assays/Travenol-Genetech Diagnostics (Cambridge, MA, USA). The determination of thyroid-stimulating hormone (TSH) has been described elsewhere (Reijnders 1985). In addition we determined serum concentrations of the free β-hCG subunit, pregnancy specific β_1-glycoprotein (SP1), human placental lactogen (hPL), dehydroepiandrosterone (DHEA) and its sulphate (DHEAS), α-fetoprotein (AFP) and cortisol, since little is known about the changes of these substances in the first trimester of pregnancy in relation to hormonal supplementation. The interassay coefficients of variation ranged between 5·4 and 9·8%. The intra-assay variabilities were <7·0%. The cross-reactivity of 17-OHP-C with the progesterone and 17-OHP assay systems was <0·01%.

Statistical methods

Statistical analyses were performed by a distribution-free test (Koziol *et al.* 1981) to compare for each variable the result of the sequence of hormone assays (response curve) in both groups in the period that 17-OHP-C was administered. To analyse the change in hormonal values during the period following administration of 17-OHP-C, the unpaired Wilcoxon test was used. For both groups estimates (after log-transformation) of the 5th and the 95th centile of the serum levels of all variables for uncomplicated singleton pregnancies in each week were calculated to compose a so-called 'response model'. This response model can be used to analyse the endocrine, ultrasonographic and clinical events in normal and pathological pregnancies (Exalto 1979).

Results

Of the 64 viable pregnancies three ended in miscarriage (two in the treatment group and one in the placebo group). There were six multiple pregnancies. In the treatment group, one infant was born preterm with severe congenital malformations and died (urethral obstruction, bladder distension, hydronephrosis).

In the uncomplicated singleton pregnancies we found statistically significantly higher mean levels of 17-OHP ($P<0\cdot001$), PRL ($P=0\cdot04$), T4 ($P = 0\cdot05$) and TBG ($P = 0\cdot02$) in the hormone supplemented group than in the placebo group (Fig. 1); the mean levels of progesterone and E2 were also higher in the hormone supplemented group than in the placebo group, but the differences were not statistically significant ($P = 0\cdot16$ and 0·26 respectively). The mean levels of hCG did not differ between the two groups ($P = 0\cdot57$). This was also found for all the other serum variables measured in the first trimester of pregnancy. After treatment with 17-OHP-C was stopped at 12 weeks gestation, the differences in the mean hormone levels between the groups remained unchanged during the next 4 weeks. The ultrasound measurements (gestational sac diameter, crown–rump length, biparietal diameter and fetal heart rate) were not influenced by the administration of 17-OHP-C as shown in Fig. 2. In the response model, the course of the hormone levels were analysed for the pregnancies that miscarried and the multiple pregnancies. In the two patients with viable pregnancies that ended in miscarriage the administration of 17-OHP-C did not prevent the decline of progesterone levels, nor the subsequent miscarriage. Serum levels of all measured hormones in the multiple pregnancies were nearly all within the range (5th–95th centile) of uncomplicated singleton pregnancies.

Discussion

In this study the prevalence of miscarriage in pregnancies with a viable fetus at 6 weeks gestation was 4·7% (95% CI 1·0 to 13·1%). The mother of the preterm baby born with severe congenital anomalies had high levels of 17-OHP (above the 95th centile of reference pregnancies) in the first trimester, but this could only partly be attributed to 17-OHP-C, as 17-OHP levels were already high before administration of 17-OHP-C.

The clinical significance of the higher maternal serum levels of 17-OHP, PRL, T4 and TBG in the first trimester after administration of 17-OHP-C could not be assessed. Furthermore, there are no theoretical grounds for expecting these higher maternal serum levels in the first trimester to have a beneficial effect on maintaining the pregnancy. Further studies are needed to investigate whether measurement of serum PRL, T4 or TBG can identify patients with a viable pregnancy who are at risk of miscarriage, since levels of these hormones can be influenced by hormonal treatment as 17-OHP-C.

Serum levels of progesterone, probably the most important hormone for the maintenance of pregnancy, were not significantly higher in the 17-OHP-C treated group than in the placebo

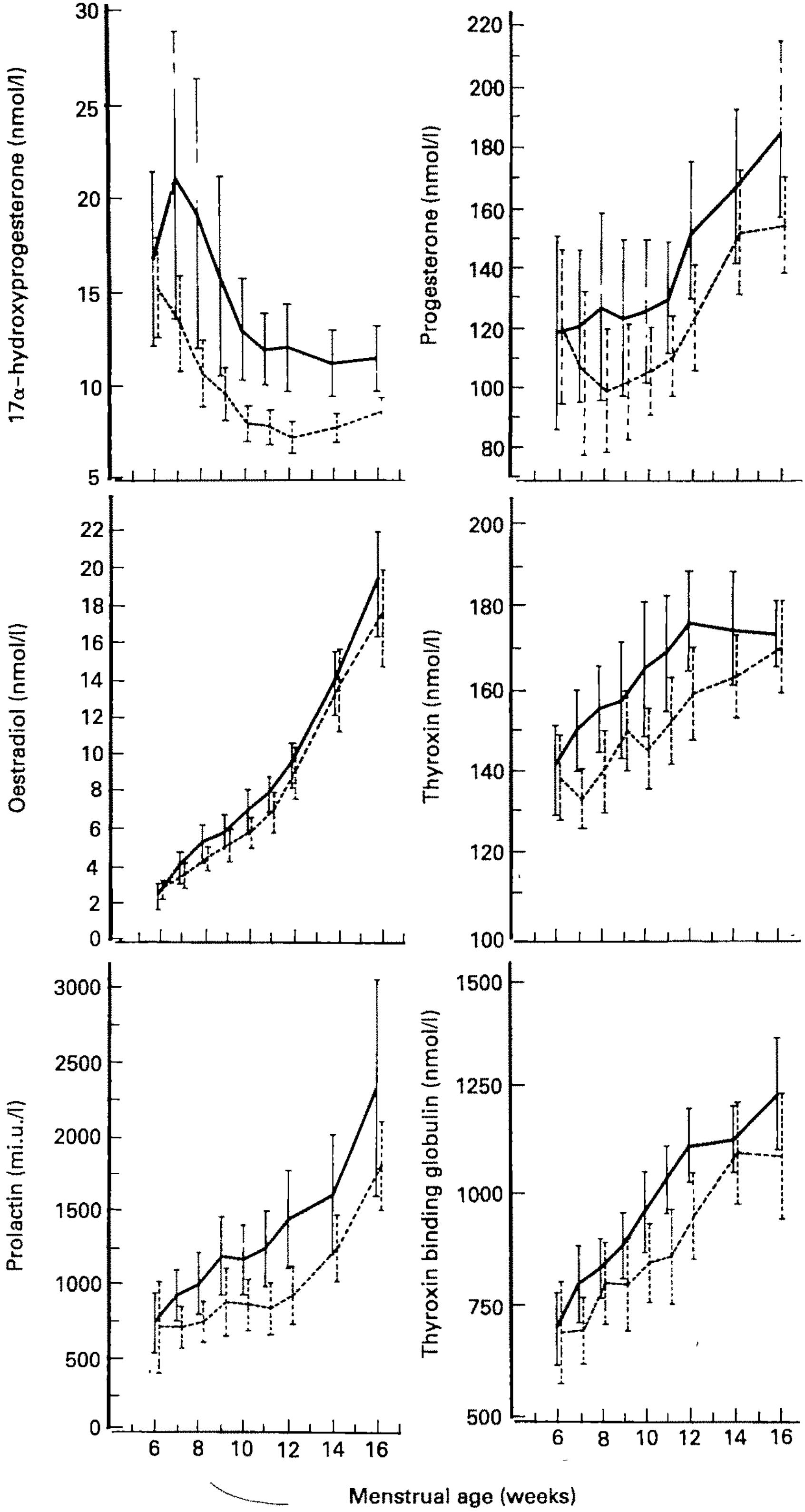

Fig. 1. Response curves of 17-OHP, progesterone, E2, T4, PRL and TBG (mean serum level ±2 SEM) in the group who received 17-OHP-C (———) and in the placebo group (– – –) during the first trimester of pregnancy.

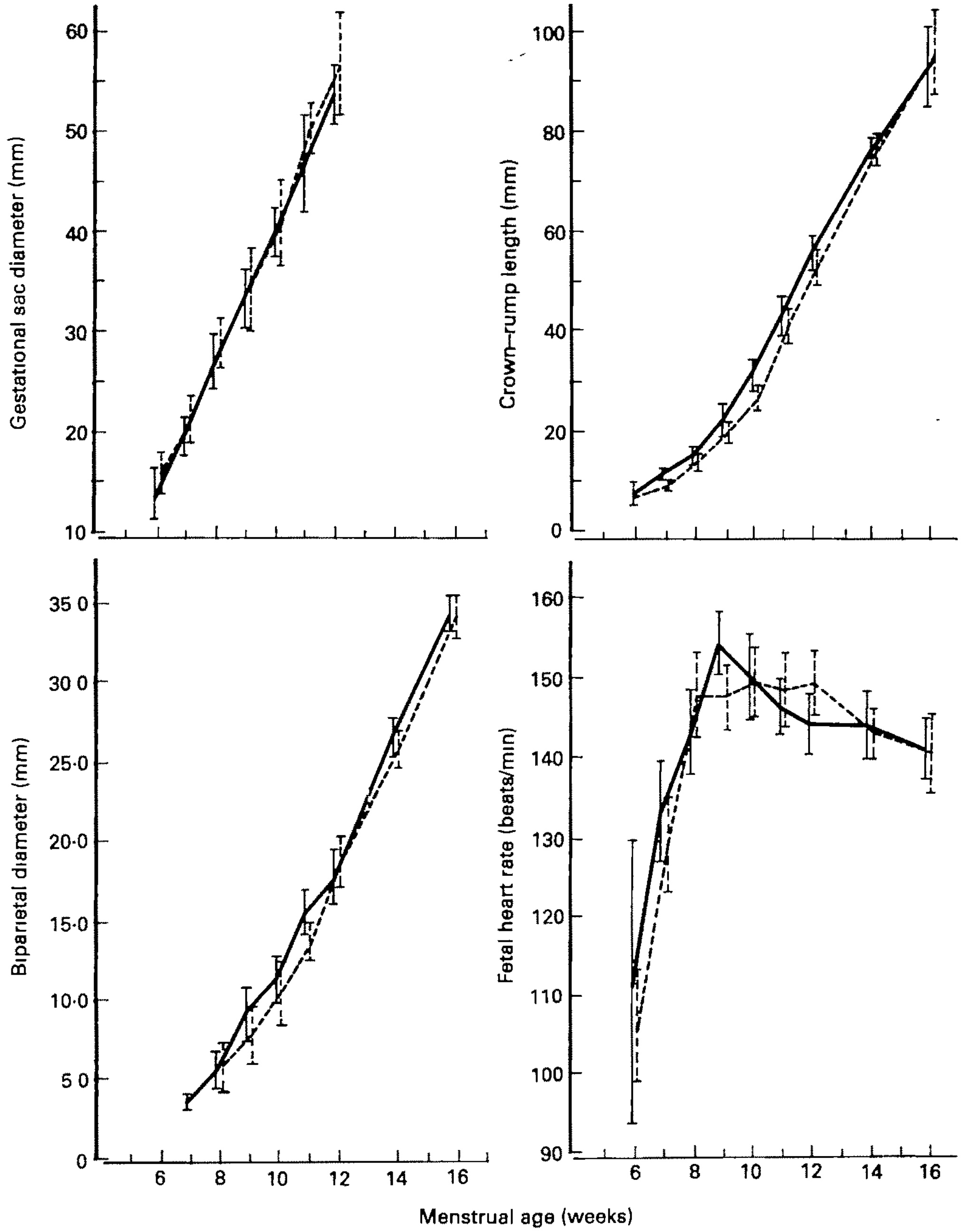

Fig. 2. Response curves of the gestational sac diameter, the fetal crown–rump length, biparietal diameter and fetal heart rate (mean ±2 SEM) in women treated with 17-OHP-C (———) and in the placebo group (– – –) during the first trimester of pregnancy.

group. Mean serum progesterone levels in the placebo group showed a nadir at 8 weeks (Fig. 1), in agreement with the phenomenon of the luteo-placental shift described by Csapo *et al.* (1972), but in the group receiving 17-OHP-C there was no such nadir. The clinical consequence of this observation could not be assessed because of the small number of patients.

In the placebo group there was a significant correlation ($P<0{\cdot}05$) between the 17-OHP and progesterone levels; women with a high serum 17-OHP level during the first trimester of pregnancy generally had a high progesterone level as well. It is questionable whether this finding in uncomplicated, high-risk pregnancies can be applied to pathological pregnancies, since 17-OHP-C treatment in two viable pregnancies that ended in miscarriage had not the expected effect on the progesterone levels.

The alterations in maternal serum hormone levels after 17-OHP-C treatment probably have no adverse effects on the child. The response curves showed no accumulation of 17-OHP in the serum with a dosage of 500 mg 17-OHP-C weekly. Maternal serum thyroxine, which was increased in the 17-OHP-C supplemented group, does not readily cross the placental barrier (Furth 1983). Besides, it has never been proven that mild hyperthyroidism has adverse effects on the developing pregnancy (Prout 1975). It is also unlikely that the elevated serum prolactin levels after administration of 17-OHP-C have adverse effects on the child (Gemzell & Wang 1979), but there is very little information on the long-term effects of progestogen treatment during pregnancy. The serious effects of exposure to diethylstilboestrol *in utero* are well known (Herbst *et al.* 1971). It is less well known that administration of stilboestrol together with ethisterone during pregnancy can also have serious long-term maternal effects, increasing the risk of breast cancer (Beral & Colwell 1980).

Administration of 17-OHP-C had no beneficial effects on the two pathological pregnancies and effected only small changes in maternal serum hormone concentrations in the uncomplicated pregnancies. Progesterone levels were on average 20% higher in the hormone supplemented group compared with the placebo group but the difference was not statistically significant. Hence it seems worthwhile to study the relation between progesterone levels and fetal outcome (miscarriage) by meta-analyses. It should be kept in mind that such studies will have to be based on a sufficiently large number of cases, probably requiring multicentre collaboration. Until then it is not advisable to prescribe 17-OHP-C in early pregnancy in order to prevent miscarriage.

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References

Anderson, S. G. (1980) Management of threatened abortion with real-time sonography. *Obstet Gynecol* **55,** 259-262.

Beral, V. & Colwell, L. (1980) Randomised trial of high doses of stilboestrol and ethisterone in pregnancy: long-term follow-up of mothers *Br Med J* **281,** 1098-1101.

Christiaens, G. C. M. L. & Stoutenbeek, Ph. (1984) Spontaneous abortion in proven intact pregnancies. *Lancet* **ii,** 571-572

Csapo, A. I., Pulkkinen, M. O., Ruttner, B., Sauvage, J. P. & Wiest, W. G. (1972) The significance of the human corpus luteum in pregnancy maintenance. *Am J Obstet Gynecol* **112,** 1061-1067

Csapo, A. I. & Pulkkinen, M O (1978) Indispensability of the human corpus luteum in the maintenance of early pregnancy luteectomy evidence *Obstet Gynecol Surv* **33,** 69-81

Dony, J. M J., Smals, A. G. H., Rolland, R., Fauser, B C. J. M & Thomas, C. M. G. (1985) Effect of aromatase inhibition by Δ^1-testolactone on basal and luteinizing hormone-releasing hormone-stimulated pituitary and gonadal hormonal function in oligospermic men. *Fertil Steril* **43,** 787-792

Edmonds, D. K , Lindsay, K. S., Miller, J. F , Williamson, E. & Wood, P. J. (1982) Early embryonic mortality in women. *Fertil Steril* **38,** 447-453.

Exalto, N. (1979) Early pregnancy. Thesis, Catholic University Nijmegen, The Netherlands.

Furth, E. D. (1983) Thyroid and parathyroid hormone function in pregnancy In *Endocrinology of Pregnancy* (Fuchs, F. & Klopper, A., eds), Harper & Row, Philadelphia, pp 176-190

Gemzell, C & Wang, C. F. (1979) Outcome of pregnancy in women with pituitary adenoma. *Fertil Steril* **31,** 363-372.

Gilmore, D. H. & McNay, M B (1985) Spontaneous fetal loss rate in early pregnancy (Letter). *Lancet* **i,** 107.

Goldzieher, J. W (1964) Double-blind trial of a progestin in habitual abortion. *JAMA* **188,** 651-654

Gustavii, B. (1984) Chorionic biopsy and miscarriage in first trimester *Lancet* **i,** 562

Herbst, A L , Ulfelder, H. & Poskanzer, D. C. (1971)

Adenocarcinoma of the vagina *N Engl J Med* **284,** 878-881.

Katz, Z., Lancet, M., Skornik, J., Chemke, J , Mogilner, B. M & Klinberg, M. (1985) Teratogenicity of progestagens given during the first trimester of pregnancy. *Obstet Gynecol* **65,** 775-780.

Koziol, J. A., Maxwell, D A , Fukushima, M., Colmerauer, M. E. & Pilch, Y. A. (1981) A distribution-free test for tumor-growth curve analyses with application to an animal tumor immunotherapy experiment. *Biometrics* **37,** 383-390.

Lauritsen, J. G. (1976) Aetiology of spontaneous abortion. *Acta Obstet Gynecol Scand* **Suppl. 52,** 1-29

Mantoni, M. (1985) Ultrasound signs in threatened abortion and their prognostic significance. *Obstet Gynecol* **65,** 471-475.

McFadyen, I. R. (1985) Missed abortion, and later spontaneous abortion, in pregnancies clinically normal at 7-12 weeks *Eur J Obstet Gynecol Reprod Biol* **20,** 381-384.

Michaelis, J , Michaelis, H , Glueck, E. & Koller, S. (1983) Prospective study of suspected associations between certain drugs administered during early pregnancy and congenital malformations. *Teratology* **27,** 57-64.

Prout, T E (1975) Thyroid disease in pregnancy *Am J Obstet Gynecol* **122,** 669-676.

Reijnders, F. J. L. (1985) The influence of 17 alpha-hydroxyprogesterone caproate on early pregnancy Thesis, Catholic University, Nijmegen, The Netherlands.

Shearman, R. P. & Garrett, W J. (1963) Double-blind study of effect of 17-hydroxyprogesterone caproate on abortion rate. *Br Med J* **ii,** 292-295.

Stirrat, G. M. (1983) Recurrent abortion—a review (Commentary). *Br J Obstet Gynaecol* **90,** 881-883.

Thomas, C. M. G., Corbey, R S. & Rolland, R. (1977) Assessment of unconjugated oestradiol and progesterone serum levels throughout pregnancy in normal women and in women with hyperprolactinaemia, who conceived after bromocriptine treatment. *Acta Endocrinol (Copenh)* **86,** 405-414.

Tognoni, G., Ferrario, L., Inzalaco, M. & Crosignani, P. G (1980) Progestagens in threatened abortion *Lancet* **ii,** 1242-1243.

van Geelen, J. M., Doesburg, W. H., Thomas, C. M. G & Martin, C. B (1981) Urodynamic studies in the normal menstrual cycle: the relationship between hormonal changes during the menstrual cycle and the urethral pressure profile. *Am J Obstet Gynecol* **141,** 384-388.

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A randomized trial of the use of cocaine spray to provide pain relief during laser vaporization of the cervix

M. G. S. MIKHAIL, J. R. BEVAN

Summary. In a double-blind trial, 50 patients undergoing laser vaporization of the cervix for cervical intraepithelial neoplasia were randomly allocated to one of two groups. One group had the cervix sprayed with 3–4 ml of a solution containing 10% cocaine, the other a placebo solution during the laser treatment. Women in the cocaine group had significantly less pain as assessed by a visual analogue scale ($P < 0{\cdot}001$) and by a verbal rating scale ($P = 0{\cdot}002$). The cocaine group also had less blood loss ($P = 0{\cdot}001$) as assessed subjectively by the operator.

Women with cervical intraepithelial neoplasia (CIN) are increasingly treated by local ablation often by CO_2 laser. This may be performed with or without anaesthesia (Table 1). Those patients without anaesthesia may experience significant discomfort (Jordan & Mylotte 1981). Local infiltration may be initially painful and cause bleeding but this last complication may be avoided by the addition of vasoactive agents (Lee *et al.* 1986).

Pain receptors in the cervix are in the form of naked nerve endings, the afferent fibres being myelinated of Aδ in type and travel through Frankenhauser's paracervical ganglia without relay into the parasympathetic system (Ganong 1981).

Their cell bodies are located in the posterior root ganglia of the second, third and fourth sacral nerves, their axons ascending in the lateral spinothalamic tracts to the postcentral gyrus (Pritchard *et al.* 1985).

Cocaine is a surface anaesthetic obtained from the leaves of *Erthroxylum coca* (Reynolds 1982). It is commonly used in ear, nose and throat surgery and when applied to mucous membranes it produces surface anaesthesia in a few minutes. Depending on the concentration this may last for 20 min or more. It is slowly absorbed because of the vasoconstriction produced, and maximum blood levels are reached some 60 min after application of a solution containing 10% cocaine to the nasal mucosa (van Dyke *et al.* 1976).

The vasoconstrictive action is used in the treatment of nose bleeds by spraying a solution onto the nasal mucosa which also enables other manoeuvres to be performed without discomfort (Ludman 1981). Because of these two effects a cocaine spray would seem to be ideally suited for cervical laser surgery.

Patients and methods

The study was a randomized prospective double-blind placebo controlled comparison of two groups of patients undergoing laser vaporization for CIN. There were 25 patients in each group. They were allocated to their groups by a computer-generated random list. In one group the cervix was sprayed with 3–4 ml of a 10% cocaine solution preserved in nipasept (a mixture of the methyl, ethyl and propyl esters of *p*-hydroxy benzoic acid). The other group was sprayed with a similar quantity of the preservative alone. There was no indication on the spray to identify the solution. Hydroxy benzoates are widely used

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St Mary's Hospital, Portsmouth
M. G. S. MIKHAIL
J. R. BEVAN

Correspondence: J. R. Bevan, Chairman, Division of Obstetrics and Gynaecology, St Mary's Hospital, Milton Road, Portsmouth PO3 6AD

Table 1. Reported techniques for pain relief employed during laser treatment of the cervix

Author	No of patients	Technique for pain relief
Lee *et al.* (1986)	50	25 local anaesthesia
		25 no analgesia or anaesthesia
Lowles *et al* (1983)	264	No analgesia or anaesthesia
Bekassy *et al.* (1983)	151	No analgesia or anaesthesia
Anderson (1982)	543	448 no analgesia or anaesthesia
		86 general anaesthesia
		9 local anaesthesia
Baggish (1982)	297	296 no analgesia or anaesthesia
		1 general anaesthesia
Burke (1982)	131	116 no analgesia or anaesthesia
		14 paracervical block
		1 general anaesthesia
Bellina *et al.* (1981)	256	No analgesia or anaesthesia
Jordan & Mylotte (1981)	91	85 no analgesia or anaesthesia
		4 general anaesthesia
		2 paracervical block
Wright & Davies (1981)	131	No analgesia or anaesthesia
Carter *et al* (1978)	45	No analgesia or anaesthesia

as a preservative; apart from some activity against moulds and fungi they are generally inert, colourless and odourless (Gucklhorn 1970) When necessary, additional pain relief was given by the local infiltration of prilocaine by hypodermic injection. All patients gave verbal consent following a description of the technique and the nature of the trial The entire transformation zone was destroyed using a Coherent system 450 CO_2 laser in the continuous mode using a spot size of 1·8 mm and a maximum power setting of 25 W. Before treatment the abnormal area was outlined by Lugol's iodine and by laser before the application of the spray because the spray caused the iodine to run. One to two millilitres of the solution were then sprayed on the cervix and repeated as necessary through the procedure. The time taken to complete the treatment, the size of the crater and an assessment of the blood loss were noted. The severity of the pain experienced was assessed at the end of the procedure using visual analogue and verbal rating scores. The visual analogue scale is a 100 mm line drawn on plain paper on which the patient marked a point on the line which corresponded to the pain experienced during the operative procedure. One end of the line represents no pain at all and the other end the worst pain imaginable (Huskisson 1983) The verbal rating scale consisted of four descriptions—none, mild, moderate or severe. Blood loss was assessed subjectively by the operator as being minimal, moderate or severe.

Statistical methods

The comparability of the two groups at randomization was tested with Student's *t*-test. All the other results were compared using the Mann–Whitney *U*-test.

Results

The two randomized groups were comparable in terms of age, parity and marital status (Table 2).

The size of the final crater was similar in the

Table 2. Characteristics of the two study groups

Variable	Cocaine spray (n = 25)	Placebo (n = 25)
Age (years)		
mean (SD)	27·4 (3·9)	26·7 (4·57)
range	21–37	19–38
Marital status		
Married	12	17
Single	10	7
Divorced	3	1
Parity		
mean (SD)	0·9 (1·24)	1 (1·00)
range	0–5	0–3

There were no significant differences between the two groups

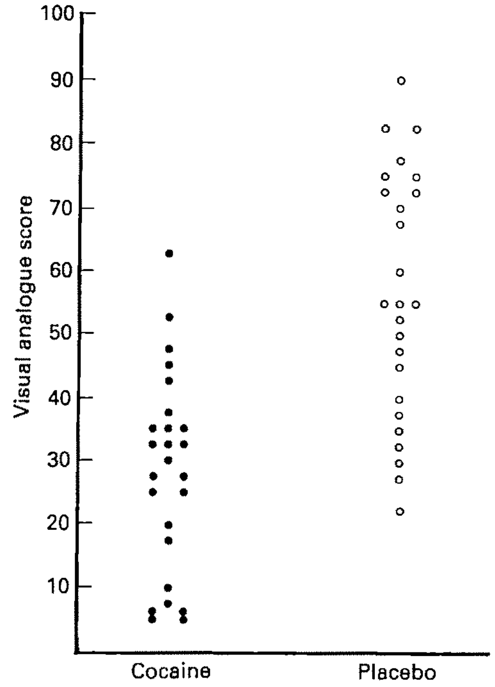

Fig. 1. Visual analogue scores for pain associated with laser vaporization of the cervix in 25 women treated with a cocaine spray and 25 treated with a placebo The pain score scale is graded from 0 (no pain at all) to 100 (the worst pain imaginable).

two groups, the mean diameter was 15·4 mm in the cocaine group and 14·8 mm in the placebo group. The mean time for completion in both groups was the same at 9 min. The pain experienced in the cocaine group was statistically significantly less when measured by the visual analogue scale ($P < 0{\cdot}001$) and also by the verbal rating scale ($P = 0{\cdot}002$) (Fig. 1, Table 3). There was significantly less bleeding in the cocaine group ($P < 0{\cdot}001$) (Table 4).

Ten patients had sufficient pain, troublesome bleeding, or both, to require additional pain relief or cryocautery to stop bleeding. All ten patients were in the placebo group. Three required only pain relief provided by prilocaine, three required additional haemostasis provided by cryocautery and four had pain and troublesome bleeding which responded again to prilocaine. There were no other observed side-effects in either group.

Discussion

The pain generated during laser vaporization is presumably the result of the heat produced as the light beam superheats intra- and extra-cellular water to 100°C with the formation of steam and subsequent evaporation of the cell (Creasman 1980). The sensation produced is variously described and probably is caused by the local build-up of heat. This can be avoided to some extent by ceasing treatment for a few seconds to allow the heat to dissipate (Bellina 1981). This study, although small in numbers, does demonstrate an easy and acceptable method of reducing the pain. The randomized and double-blind nature of the trial eliminated observer bias.

Bleeding is a well-recognized complication of this form of surgery; Anderson (1982) reported that up to 7% of 543 patients required some additional attention and that hospital admission was needed in 1·1%. Similarly, Baggish (1982) treated 297 patients using a dilute solution of vasopressin injected into the cervix to reduce blood loss. Despite these measures 37 patients required further therapy, and packing or suture was necessary in seven. Cocaine is able to prevent haemorrhage through its powerful vasoconstrictive action.

Although no side-effects of note were encountered in this series, it might be possible for excessive amounts of cocaine to cause symptoms of central nervous system overstimulation and sympathetic overactivity (Cohen 1975). Cardiovascular effects are of short duration and are usually limited to a sinus tachycardia (Fennel 1976). Cocaine and adrenaline enhance each other's sympathomimetic actions and should not be used in conjunction. Cocaine idiosyncrasy is rare but Reynolds (1982) suggested that a test dose should be given before the spray is used on the mucous membranes. Nevertheless, it has been used before intubation in patients undergoing coronary artery surgery (Barash 1980).

Cocaine is a controlled drug, and a register of its use must therefore be kept in the clinic. The solution should be kept protected from light but

Table 3. Distribution of verbal pain scores associated with laser vaporization of the cervix in two groups

Pain score	Cocaine spray ($n = 25$)	Placebo ($n = 25$)
None	3	—
Mild	10	4
Moderate	12	14
Severe	—	7

Table 4. Distribution of bleeding scores associated with laser vaporization of the cervix in two groups

Bleeding score	Cocaine spray ($n = 25$)	Placebo ($n = 25$)
Minimal	23	8
Moderate	2	6
Troublesome	—	11

it remains stable at room temperature for about 1 year.

The only disadvantage encountered was the action the solution had on Lugol's iodine but this can be countered by marking the area to be treated before spraying.

It can no longer be acceptable to perform laser vaporization without the use of adequate pain relief when necessary. The cocaine spray combines ease of use with good analgesia and vasoconstrictive actions. The discomfort of local anaesthetic injections is also avoided.

References

Anderson, M. (1982) Treatment of cervical intraepithelial neoplasia with the carbon dioxide laser. Reports of 543 patients. *Obstet Gynecol* **59**, 720-725.

Baggish, M. S. (1982) Management of cervical intraepithelial neoplasia by carbon dioxide laser. *Obstet Gynecol* **60**, 378-384

Barash, P. G. (1980) Is cocaine a sympathetic stimulant during general anaesthesia? *JAMA* **243**, 1437-1439.

Bekassy, Z., Alm, P., Gundell, H., Larsson, G. & Astedt, B. (1983) Laser microconization in mild and moderate dysplasia of the uterine cervix *Gynecol Oncol* **15**, 357-362.

Bellina, J. H., Wright, V. C., Voros, J. I., Riopelle, M. A. & Hohenschutz, V (1981) Carbon dioxide laser management of cervical intraepithelial neoplasia. *Am J Obstet Gynecol* **141**, 828-832.

Burke, L. (1982) The use of the carbon dioxide laser in the therapy of cervical intraepithelial neoplasia. *Am J Obstet Gynecol* **144**, 337-340

Carter, R., Krantz, K E., Hara, G. S., Lin, F., Masterson, B. J. & Smith, S. J. (1978) Treatment of cervical intraepithelial neoplasia with the carbon dioxide laser beam. *Am J Obstet Gynecol* **131**, 831-836.

Cohen, S. (1975) Cocaine. *JAMA* **231**, 74-75

Creasman, W. T (1980) Conservative management of cervical intraepithelial neoplasia. *Clin Obstet Gynecol* **23**, 281-291.

Fennel, W. H. (1976) Cardiovascular effects of cocaine *N Engl J Med* **295**, 960-961.

Ganong, W F. (1981) *Review of Medical Physiology.* 10th edn, Lange Medical Publications, Los Altos, pp. 100-106.

Gucklhorn, I. R. (1970) A review of antimicrobial agents, including hydroxy benzoates, used in cosmetics *J Manufacturing Chem* **41**, 50.

Huskisson, E. C. (1983) *Pain Measurement and Assessment.* Raven Press, New York, pp. 33-37

Jordan, J. A. & Mylotte, J (1981) Treatment of CIN by destruction-laser. In *Preclinical Neoplasia of the Cervix* (Jordan, J. A., Sharp, F. & Singer, A , eds), Proceedings of the Ninth Study Group of the Royal College of Obstetricians and Gynaecologists, London, pp. 205-211

Lee, E. T C., Ozumba, E N & Bevan, J. R. (1986) A randomized trial of citanest with octopressin for relief of pain associated with laser vaporization of the cervix *Br J Obstet Gynaecol* **93**, 967-969

Lowles, I. E , Al-Kurdi, M & Hare, M. J. (1983) Women's recollection of pain during and after carbon dioxide laser treatment to the uterine cervix. *Br J Obstet Gynaecol* **90**, 1157-1159.

Ludman, H. (1981) Nose bleeds. *Br Med J* **282**, 967-969.

Pritchard, J., MacDonald, P & Grant, N. (eds) (1985) *Williams Obstetrics.* 17th edn, Appleton-Century-Crofts, New York, p. 20.

Reynolds, J. (1982) *Martindale—The Extra Pharmacopoeia.* 28th edn, The Pharmaceutical Press, London, pp 914-916

van Dyke, C., Barash, P. G. & Jatlow, P. (1976) Cocaine plasma concentrations after intranasal application in man. *Science* **191**, 859-861.

Wright, V. C. & Davies, E. M. (1981) The conservative management of cervical intraepithelial neoplasia by the use of cryosurgery and the carbon dioxide laser. *Br J Obstet Gynaecol* **88**, 663-668

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The blood flow velocity waveform in the fetal internal carotid and umbilical artery; its relation to fetal behavioural states in the growth retarded fetus at 37–38 weeks gestation

J. VAN EYCK, J. W. WLADIMIROFF, M. J. NOORDAM,
J. A. G. W. VAN DEN WIJNGAARD, H. F. R. PRECHTL

Summary. In eight women whose fetuses showed evidence of intrauterine growth retardation (IUGR), the relation was examined between the blood flow velocity waveform in the fetal internal carotid and umbilical artery and fetal behavioural states at 37–38 weeks gestation. In both vessels there was a virtual overlap of pulsatility index values originating from state 1F and 2F, reflecting behavioural state independency. In the internal carotid artery this state independency is associated with moderately reduced pulsatility index values.

Nijhuis *et al.* (1982) were the first to provide clear evidence for the existence of behavioural states in the human fetus during the last weeks of pregnancy. It was demonstrated in previous studies that in normal pregnancies at 37–38 weeks gestation, blood flow velocity waveforms in the lower thoracic part of the fetal descending aorta (van Eyck *et al.* 1985) and internal carotid artery (van Eyck *et al.* 1987) are affected by these behavioural states. In the umbilical artery no such state dependency could be established, suggesting a fetal origin of the observed aortic and carotid blood flow changes (van Eyck *et al.* 1987). In intrauterine growth retardation (IUGR), flow velocity waveform changes have been reported in the fetal descending aorta, umbilical artery and internal carotid artery, suggesting the presence of increased peripheral vascular resistance at the fetal trunk and placental level (Griffin *et al.* 1983; Reuwer *et al.* 1984; Trudinger *et al.* 1985; Tonge *et al.* 1986) associated with reduced vascular resistance in the fetal cerebrum (Wladimiroff *et al.* 1986). In contrast to normal pregnancy, there was no state dependency in the fetal descending aorta in IUGR (van Eyck *et al.* 1986). The object of the present study was to establish whether state independency was also present in the fetal internal carotid artery and umbilical artery in pregnancies complicated by IUGR.

Patients and methods

A total of eight patients with IUGR in singleton pregnancies at 37–38 weeks gestation gave consent to participate in the study. The gestational age had been calculated from a reliable men-

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Department of Obstetrics and Gynaecology, Erasmus University, The Netherlands
J. VAN EYCK
J. W. WLADIMIROFF
M. J NOORDAM
J A. G W. VAN DEN WIJNGAARD

Department of Developmental Neurology, Academic Hospital, Groningen, The Netherlands
H F. R. PRECHTL

Correspondence: J. W. Wladimiroff, MD, Professor of Obstetrics and Gynaecology, Academic Hospital Rotterdam-Dijkzigt, Erasmus University Rotterdam, Dr Molewaterplein 40, 3015 GD Rotterdam, The Netherlands

strual history and early ultrasonic measurement of fetal crown–rump length or biparietal diameter. IUGR was defined as a progressive asymmetrical slow-down in increase of fetal head and upper abdominal circumference resulting in values below the 5th centile of the nomograms by Campbell & Wilkin (1975). Five out of eight patients had a raised diastolic blood pressure (>90 mmHg). No medication was prescribed. There was no serological evidence of fetal infection. There were no signs of fetal distress during the behavioural studies. Gestational age at delivery ranged between 39 and 41 weeks. Fetal distress, diagnosed by late FHR decelerations during labour, occurred in six patients resulting in caesarean section in four and forceps extraction or fundal expression in the remaining two patients. Fetal birthweight was below the 5th centile for gestational age according to the tables of Kloosterman (1970), adjusted for parity and fetal sex. There were no congenital abnormalities. Apgar scores were ≥5 at 1 min and ≥8 at 5 min in all eight infants. All patients were studied in the semirecumbent position. A combined mechanical sector scanner and pulsed Doppler system (Diasonics CV 400) was used for recording maximum flow velocity waveforms in the fetal internal carotid and umbilical artery during fetal behavioural states 1F (quiet sleep) and 2F (active sleep) as described by Nijhuis *et al.* (1982).

To establish these fetal behavioural states, the following variables were recorded simultaneously: (i) The fetal heart rate (FHR), which was obtained from a Doppler ultrasound cardiotocograph (Hewlett Packard 8040A, carrier frequency 1 MHz); (ii) fetal eye movements which were studied from a transverse view of the fetal face using the Diasonics CV 400 (carrier frequency 3·5 MHz); (iii) fetal body movements which were obtained from a sagittal view of the fetal trunk, using a two-dimensional real-time linear array scanner (Toshiba Sal 20A, carrier frequency 3·5 MHz). The three transducers were placed in such a way that there was minimal interference between the three ultrasound modes. We found a stable combination of the three state variables with short transitions within 3 min. Our patients therefore displayed true behavioural states and not just coincidence of the variables. Flow velocity recordings were only performed when a clear fetal behavioural state was identified and when this state had been present over a period of at least 3 min. All recordings were started 2 h after the evening meal and were performed during fetal apnoea. The maximum amount of time allowed between a state determination and the completion of a flow velocity recording was 3 min. Blood flow velocity waveforms were recorded on videotape over a 15-s period which included an average of 20 consecutive cardiac cycles. In each subject a minimum of three flow velocity waveform recordings in each vessel in each behavioural state (1F and 2F) was obtained. From hard copies of each flow velocity recording an average of 15 cardiac cycles of optimal quality were selected. The degree of pulsatility of the waveform was quantified by calculating the pulsatility index (PI) according to Gosling & King (1975) using a microcomputer. Cardiac cycle dependency of the PI was ruled out by dividing the PI values in each subject and for each fetal behavioural state into groups, each of which represented a FHR range of 5 beats/min. Changes in PI values with respect to the fetal behavioural state were tested using the paired Student's *t*-test and the 95% confidence interval. The relation between PI and FHR was tested by analysing the slopes of the individual regression lines by Student's *t*-test.

Results

The mean number of cardiac cycles studied in the fetal internal carotid artery for all eight subjects was 50 (range 31–72) in state 1F and 48 (range 29–63) in state 2F, a total of 782 cycles. FHR in state 1F ranged between 98 and 158 beats/min and in state 2F between 115 and 167 beats/min. When calculating the mean PI independent of FHR and behavioural state, all eight values were below −1 SD and in two patients below −2 SD of the nomogram of Wladimiroff *et al.* (1987).

The mean number of cardiac cycles studied in the umbilical artery was 47 (range 15–66) in state 1F and 41 (range 18–62) in state 2F, a total of 699 cycles. FHR in state 1F ranged between 99 and 171 beats/min and in state 2F between 107 and 162 beats/min. The mean PI irrespective of FHR and behavioural state was above +1 SD in all eight patients and above +2 SD in five patients according to the nomogram by Wladimiroff *et al.* (1987).

Paired analysis of the PI data in state 1F and 2F was feasible for the fetal internal carotid artery in the FHR range between 126 and 145

Table 1. Mean paired pulsatility index (PI) difference (ΔPI±1 SD) and 95% confidence interval between fetal behavioural states 1F and 2F in the fetal heart rate (FHR) range between 126 and 145 beats/min in the fetal internal carotid artery in fetal growth retardation

FHR range (beats/min)	Number of paired observations	Mean PI State 1F	Mean PI State 2F	ΔPI	SD	Significance (*P*)	95% confidence interval
126–130	7	1·09	1·14	−0·05	0·28	>0·20	−0·31 to 0·21
131–135	7	1·05	1·14	−0·09	0·22	>0·20	−0·29 to 0·11
136–140	8	1·01	1·07	−0·06	0·18	>0·20	−0·21 to 0·09
141–145	7	0·97	1·10	−0·13	0·21	>0·10	−0·33 to 0·07

beats/min (561 cardiac cycles) and for the umbilical artery also in the FHR range between 126 and 145 beats/min (529 cardiac cycles). There was no statistically significant difference in mean PI between state 1F and 2F for all FHR range studies in the fetal internal carotid artery (Table 1) and umbilical artery (Table 2). Moreover, the 95% confidence interval of the paired differences in mean PI between state 1F and 2F displayed for each FHR range a narrow distribution around zero, reflecting a virtual overlap of PI values originating from state 1F and 2F. Figure 1 demonstrates for the fetal internal carotid artery and umbilical artery the regression lines for the relation between PI and FHR in state 1F and 2F for all eight subjects. The length of the lines indicates the range of the observed data. A significant inverse relation between PI and FHR was established for both behavioural states 1F ($P<0{\cdot}001$) and 2F ($P<0{\cdot}01$) in the umbilical artery and for behavioural state 1F ($P<0{\cdot}001$) in the fetal internal carotid artery.

Discussion

All eight fetuses in the present study displayed growth retardation expressed by asymmetric slow-down in increase of fetal head and upper-abdominal circumference and a birthweight below the 5th centile for gestational age.

Although there were no signs of fetal distress at the time of the behavioural studies, six fetuses displayed abnormal heart rate patterns during labour resulting in assisted vaginal delivery or caesarean section. True fetal behavioural states were established in all eight pregnancies, similar to an earlier study in which well-defined behavioural states were related to blood flow in the fetal descending aorta during IUGR (van Eyck *et al.* 1986).

Recently, flow measurements in the fetal internal carotid artery of normal pregnancies demonstrated reduced PI values during state 2F, reflecting a decrease in cerebral vascular resistance during this behavioural state (van Eyck *et al.* 1987). The present study suggests that this state dependency is absent during IUGR. Similar observations in the fetal descending aorta in IUGR (van Eyck *et al.* 1986), showed that state independency was nearly always associated with markedly raised PI values. It was suggested that state dependency in this vessel is overruled by stimulation of peripheral chemoreceptors and subsequent release of vasoconstrictor agents, such as vasopressin and catecholamines. In contrast to the marked PI

Table 2. Mean paired pulsatility index (PI) difference (ΔPI±1 SD) and 95% confidence interval between fetal behavioural states 1F and 2F in the fetal heart rate (FHR) range between 126 and 145 beats/min in the umbilical artery in fetal growth retardation

FHR range (beats/min)	Number of paired observations	Mean PI State 1F	Mean PI State 2F	ΔPI	SD	Significance (*P*)	95% confidence interval
126–130	5	1·13	1·17	−0·04	0·15	>0·20	−0·23 to 0·15
131–135	6	1·26	1·27	−0·01	0·10	>0·20	−0·11 to 0·09
136–140	7	1·24	1·23	0·01	0·13	>0·20	−0·11 to 0·13
141–145	6	1·20	1·19	−0·01	0·13	>0·20	−0·15 to 0·13

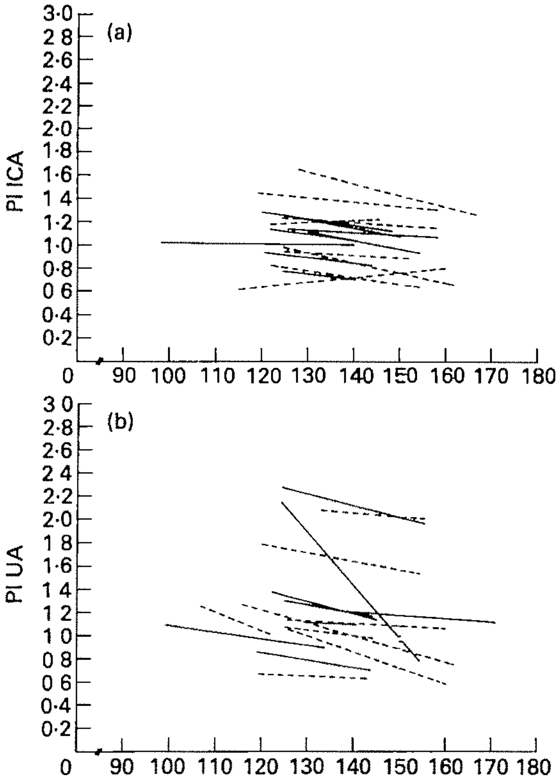

Fig. 1. Regression lines for the correlation between pulsatility index (PI) and fetal heart rate (FHR) in fetal behavioural states 1F (——) and 2F (- - -) in the fetal internal carotid artery (ICA) (a) and umbilical artery (UA) (b) for all eight pregnancies with fetal growth retardation

increase in the fetal descending aorta, state independency in the fetal internal carotid artery was associated with only moderate reduction in PI, suggesting the onset of circulatory redistribution with the aim of favouring cerebral blood flow (brain sparing effect). The degree of PI reduction at this stage seems, however, to be sufficient to overrule behavioural state dependency. Whereas in the fetal internal carotid artery and descending aorta, blood flow velocity patterns changed from state dependency in normal pregnancy into state independency in IUGR, blood flow velocity patterns in the umbilical artery displayed behavioural state independency both in normal pregnancy and IUGR. This strongly suggests a fetal origin of the behavioural state related changes in aortic and carotid blood flow. The inverse relation between PI and FHR for both state 1F and 2F in the umbilical artery and for state 1F in the fetal internal carotid artery is mainly determined by the cycle dependency of the formula from which the PI is calculated. This cycle length dependency is mainly due to changes in end diastolic velocity in relation to FHR (van Eyck *et al.* 1985). The differences between umbilical and internal carotid artery with respect to the statistical significance of the inverse correlation between PI and FHR can be explained by the lower absolute PI values in the latter vessel resulting in a reduced slope of the regression line. This is in agreement with earlier studies in the fetal internal carotid artery, descending aorta and umbilical artery (van Eyck *et al.* 1985, 1986, 1987), in which higher PI values are associated with steeper slopes, the steepest slope of the regression line being established in the fetal descending aorta during IUGR.

It can be concluded, that in the presence of IUGR, blood flow in the fetal internal carotid and umbilical artery is behavioural state independent. In the internal carotid artery this state independency is associated with only moderate reduction in PI.

References

Campbell, S. & Wilkin, D. (1975) Ultrasonic measurement of fetal abdomen circumference in the estimation of fetal weight. *Br J Obstet Gynaecol* **82,** 689-697

Gosling, R. G. & King, D. H. (1975) Ultrasound angiology. In *Arteries and Veins* (Marcus, A. W. & Adamson, L., eds), Churchill Livingstone, Edinburgh, pp. 61-98

Griffin, D., Cohen-Overbeek, T & Campbell, S (1983) Fetal and uteroplacental blood flow *Clin Obstet Gynaecol* **10,** 565-602

Kloosterman, G. (1970) On intrauterine growth. The significance of prenatal care. *J Int Gynaecol Obstet* **8,** 895-912.

Nijhuis, J. G , Prechtl, H. F R., Martin, Jr C. B. & Bots, R. S. G. M (1982) Are there behavioural states in the human fetus? *Early Hum Dev* **6,** 177-195.

Reuwer, P J H. M., Bruinse, H. W., Stoutenbeek, Ph & Haspels, A. A (1984) Doppler assessment of the fetoplacental circulation in normal and growth retarded fetuses. *Eur J Obstet Gynecol Reprod Biol* **18,** 199-207

Tonge, H. M , Wladimiroff, J. W , Noordam, M. J. & van Kooten, C. (1986) Blood flow velocity waveforms in the descending aorta of the fetus in the third trimester of pregnancy: a comparison between normal and growth retarded pregnancies *Obstet Gynecol* **67,** 851-855.

Trudinger, B. J., Giles, W B., Cook, C. M., Bombardieri, J. & Collins, L. (1985) Fetal umbilical artery flow velocity waveforms and placental resistance: clinical significance. *Br J Obstet Gynaecol* **92,** 23-30.

van Eyck, J., Wladimiroff, J. W., Noordam, M J., Tonge, H. M. & Prechtl, H. F. R. (1985) The blood flow velocity waveform in the fetal descending aorta; its relationship to fetal behavioural states in normal pregnancy at 37-38 weeks. *Early Hum Dev* **12,** 137-143

van Eyck, J., Wladimiroff, J. W., Noordam, M. J., Tonge, H. M. & Prechtl, H F. R. (1986) The blood flow velocity waveform in the fetal descending aorta; its relationship to behavioural states in the growth retarded fetus at 37-38 weeks of gestation. *Early Hum Dev* **14,** 99-107.

van Eyck, J., Wladimiroff, J. W., van den Wijngaard, J. A G. W., Noordam, M. J & Prechtl, H. F. R. (1987) The blood flow velocity waveform in the fetal internal carotid and umbilical artery; its relation to fetal behavioural states in normal pregnancy at 37–38 weeks of gestation. *Br J Obstet Gynaecol* **94,** 736-741

Wladimiroff, J. W., Tonge, H M. & Stewart, P. A. (1986) Doppler ultrasound assessment of cerebral blood flow in the human fetus. *Br J Obstet Gynaecol* **93,** 471-475.

Wladimiroff, J. W., van den Wijngaard, J. A G. W., Degani, S., Noordam, M. J., van Eyck, J. & Tonge, H. M. (1987) Cerebral and umbilical arterial blood flow velocity waveforms in normal and growth-retarded pregnancies; a comparative study. *Obstet Gynecol* **69,** 705-709.

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Umbilical artery flow velocity waveforms in fetuses dying with congenital anomalies

FON-JOU HSIEH, FONG-MING CHANG, TSANG-MING KO, HSI-YAO CHEN, YUAN-PING CHEN

Summary. Absent or reversed diastolic component in umbilical artery (UA) flow velocity waveform was observed in eight fetuses with major malformations. Because of the uncorrectable fetal conditions or the parents' reluctance to terminate the pregnancy, no interventions were undertaken and eventually all eight fetuses died *in utero*. The interval between the abnormal waveform recording and fetal death was between 1 and 7 days (mean 3·6 days). In two fetuses with abnormal diastolic flow, analysis of umbilical vein blood obtained by ultrasound-guided sampling revealed moderately severe acidosis and hypoxia (pH 7·228 and 7·241, $P\text{CO}_2$ 47·5 and 46·9 mmHg; $P\text{O}_2$ 14·6 and 14·7 mmHg, respectively). Our observation suggests that once the diastolic component of UA flow velocity waveforms becomes absent or reversed, the fetus is in a state of hypoxia and acidosis and fetal death is impending. This limited experience may help in formulating clinical management when using UA flow velocity waveforms in the monitoring of high-risk fetuses.

Several reports have suggested that the umbilical artery (UA) flow velocity waveform could be a promising tool for fetal surveillance (Friedman *et al.* 1985; McCallum *et al.* 1978; Schulman *et al.* 1984; Stuart *et al.* 1981; Trudinger *et al.* 1985c). For conventional methods of fetal surveillance, such as the oxytocin challenge test (Huddleston & Freeman 1977; Ray *et al.* 1972), the timing of delivery is relatively well established, but for UA waveform patterns this 'point of action' remains unknown. This information is not easy to obtain, since it is increasingly difficult to withhold the UA waveform data from clinicians responsible for management.

In our study of UA velocity waveforms, eight pregnancies ended in intrauterine fetal death shortly after the UA waveform was recorded and the present report analyses these UA waveforms. From this we hope to define the 'point of action' for this new mode of fetal surveillance.

Patients and methods

Between October 1985 and December 1986, eight pregnancies in our UA flow velocity waveform study ended in intrauterine fetal death. All fetuses had major congenital anomalies. Amniocentesis or ultrasound-guided fetal blood sam-

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Antenatal Diagnostic Center, Department of Obstetrics and Gynecology, College of Medicine and the Hospital of National Taiwan University, Taipei, Taiwan 10016, Republic of China
FON-JOU HSIEH *Associate Professor*
FONG-MING CHANG *Senior Resident*
TSANG-MING KO *Lecturer*
HSI-YAO CHEN *Professor*
YUAN-PING CHEN *Professor*

Correspondence: F J. Hsieh, Associate Professor, Department of Obstetrics and Gynecology, National Taiwan University Hospital, Taipei, Taiwan 10016, Republic of China

Table 1. Clinical data of fetuses with abnormal umbilical artery flow velocity waveforms (UAFVW) and fetal death

Patient no.	Maternal age (years)	G+P	Ultrasound finding	GA at UAFVW (week + day)	UAFVW finding	NST	Karyotype	Fetal outcome	BW (g)	PW (g)	Interval between abnormal UAFVW and IUD (days)	Final diagnosis
1	28	1+0	Fetal arrhythmia Hydrops fetalis CHD	23+0	Absent diastolic velocity	NR	46, XX	IUD	1200	500	4	CHD (VSD+PS)
2	25	5+2	Hydrops fetalis	27+6	Absent diastolic velocity	NR	46, XX	IUD	580	700	4	Hb Bart's hydrops fetalis
3	25	1+0	IUGR CHD	38+4	Absent diastolic velocity	NR	46, XX/47, XX, +18	IUD	1250	250	3	Trisomy 18 mosaicism
4	25	1+0	Fetal arrhythmia IUGR Polyhydramnios VSD	34+6	Absent diastolic velocity	NR +Spontaneous deceleration	47, XX, +18	IUD	1080	110	1	Trisomy 18
5	33	4+3	Hydrops fetalis CHD	31+6	Absent diastolic velocity	NR	46, XX	IUD	1050	550	5	CHD (ASD+VSD)
6	28	1+0	Holoprosencephaly	29+0	Absent diastolic velocity	R	46, XY, −13, +t(13;13)	IUD	1280	300	4	Trisomy 13q
7	23	1+0	Hydrops fetalis	28+5	Absent diastolic velocity	NR	—	IUD	NA	NA	1	Hb Bart's hydrops fetalis
8	29	1+0	IUGR Polyhydramnios	34+0	Reversed diastolic velocity	NR	46, XX/47, XX, +18	IUD	950	250	7	Trisomy 18 mosaicism

G, Gravidity; P, parity, GA, gestational age; IUGR, intrauterine growth retardation; CHD, congenital heart disease; NST, non-stress test; R, reactive; NR, non-reactive; IUD, intrauterine fetal death, Hb Bart's, hemoglobin Bart's; NA, not available (because delivered by local practitioner); BW, birthweight; PW, placental weight; ASD, atrial septal defect; VSD, ventricular septal defect; PS, pulmonary stenosis.

pling (Hsieh *et al.* 1987; Nicolaides *et al.* 1986) were performed in all of them to establish karyotypes or haematological status. Because of untreatable conditions, such as trisomy 13, 18, or haemoglobin Bart's hydrops fetalis, or parents' reluctance to have the pregnancy terminated, all the fetuses eventually died *in utero*. All these decisions had been accepted by the parents after thorough counselling.

Umbilical artery flow velocity waveform study and cardiotocography were performed at the time of initial diagnosis. Fetal death was confirmed by follow-up ultrasound. The UA flow velocity waveforms were obtained using a Duplex system (Aloka SSD-280 and UGR-23, Tokyo, Japan) or a continuous-wave Doppler unit (DMS, Spectrodop, France). The thump fiter ranges used were 200 Hz for the Aloka system and 100 Hz for the DMS unit.

In the last two patients, umbilical vein blood samples were obtained with an ultrasound-guided needle and were immediately sent for blood gas and acid-base analysis using a Radiometer ABL-2C (Copenhagen).

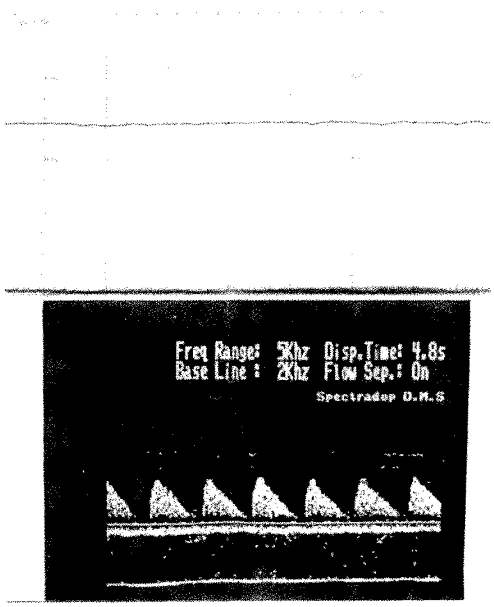
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Fig. 1. (Above) Actocardiograph in a fetus (no. 7) with haemoglobin Bart's hydrops fetalis at 28 weeks gestation recorded one day before death *in utero*. The upper channel shows the non-reactive fetal heart rate tracing and the lower channel the fetal movement record. (Below) Umbilical artery flow velocity waveforms showing absent diastolic component.

Results

The clinical details, final diagnosis, UA flow velocity waveforms, cardiotocographic findings, and the interval between UA velocimetry and fetal death are given in Table 1.

The underlying fetal conditions included congenital heart disease in two, haemoglobin Bart's hydrops fetalis in two and trisomy in four fetuses. All the fetuses had zero or reversed diastolic component in their UA waveforms. Fetal heart rate (FHR) patterns were all non-reactive with or without decelerations except in patient no. 6. Figures 1 and 2 show the UA waveforms and FHR patterns in patients nos 7 and 8. Umbilical vein blood samples from patients 7 and 8 showed moderately severe acidosis and hypoxia as illustrated in Fig. 3.

The interval between the UA flow velocity waveform study and fetal death ranged from 1 to 7 days (average 3·6 days).

Discussion

We do not know of any published studies that deal solely with the UA waveforms of dying fetuses. This information is of vital importance if UA waveform analysis is to be used for antepartum fetal surveillance. Although UA flow velocimetry data have been valuable in the management of growth-retarded fetuses (Erskine & Ritchie 1985; FitzGerald *et al.* 1984; Fleischer *et al.* 1985; Trudinger *et al.* 1985*b*,*c*), diabetic pregnancy (Bracero *et al.* 1986; Trudinger *et al.* 1985*a*), twin pregnancy (Farmakides *et al.* 1985; Giles *et al.* 1985*b*) and pre-eclampsia (Friedman *et al.* 1985), only a few studies have reported UA velocimetry data in association with fetal death. Schulman *et al.* (1984) described the intrauterine death of a 2835 g fetus in an uncomplicated pregnancy except for an umbilical artery systolic/diastolic ratio (A/B ratio) of 3·7. The interval between the abnormal UA waveform and fetal death was not reported. Friedman *et al.* (1985) reported two intrauterine deaths within 1 and 2 weeks after the recording of abnormal UA waveforms in two women with sickle cell anaemia and systemic lupus erythematosus respectively.

In a study of UA waveforms in pregnancies with major fetal malformations, Trudinger & Cook (1985) reported three stillbirths among 13 malformed fetuses with abnormal UA waveforms, also one intrauterine death which

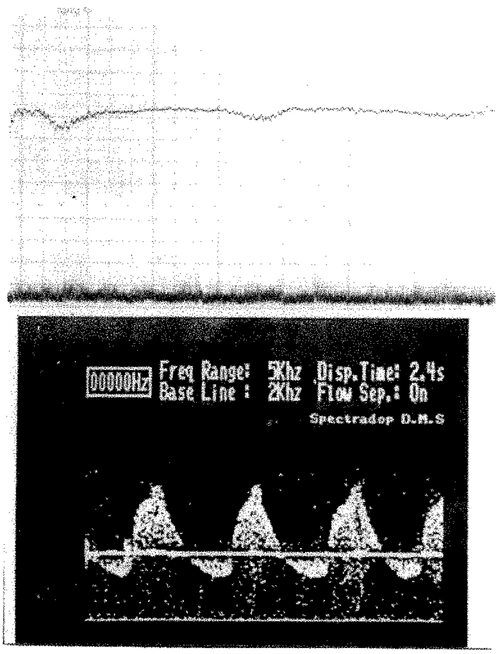
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Fig. 2. (Above) Actocardiograph in a fetus (no. 8) with trisomy 18 mosaicism at 34 weeks gestation recorded 7 days before death *in utero*. The upper channel shows the non-reactive fetal heart rate tracing and the lower channel the fetal movement record. (Below) The abnormal umbilical artery flow velocity waveforms showed reversed diastolic flow.

occurred 5 days after the recording of a waveform with total absence of diastolic flow. Erskine & Ritchie (1985) described two intrauterine deaths in hypertensive pregnancies in association with zero diastolic components of the UA waveforms but they did not specify the intervals between the abnormal recordings and the fetal deaths. In a recent study of UA waveforms in diabetic pregnancy, Bracero *et al.* (1986) described two fetal intrauterine deaths, one fetus had an umbilical artery A/B ratio of 5·1 at 37 weeks gestation and, in spite of a reactive NST, the fetus died at 40 weeks gestation, the birthweight was 4760 g. The other fetus had an umbilical artery A/B ratio of 3·7 at 35 weeks gestation and died *in utero* at 36 weeks (birthweight 2250 g).

Nicolaides *et al.* (1986) reported a 33-week fetus with severe symmetrical intrauterine growth retardation. Reversed diastolic flow in the umbilical artery was observed and cord blood gas analysis revealed severe acidosis and hypoxia. The fetus was saved by emergency caesarean section. The two fetuses sampled *in utero* in our study also showed hypoxia and acidosis.

From our results and a review of the literature, we may speculate that by the time the diastolic component of UA flow velocity waveform becomes absent or reversed, the fetus is acidotic and hypoxic and at high risk of death *in utero*. We therefore postulate that in a compromised fetus, loss of diastolic flow in the UA circulation will precede fetal death. However, the interval between absent diastolic flow and fetal death remains to be defined. From our series, this interval may range from 1 to 7 days, but our observations are based exclusively on fetuses with severe congenital anomalies and may not be applicable to fetuses without malformation.

At present, cardiotocography is the mainstay of antenatal fetal surveillance. It had been sug-

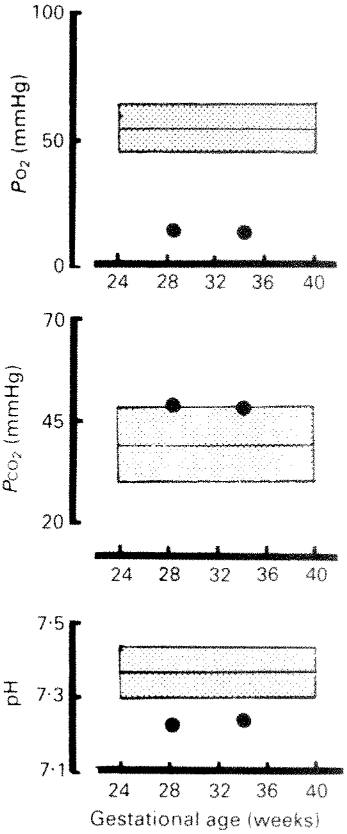

Fig. 3. Blood gases and pH in umbilical vein blood samples (●) in two fetuses (nos 7 and 8) with abnormal umbilical artery flow velocity waveforms, plotted against normal ranges from Nicolaides *et al.* (1986) (▨).

gested that abnormal UA waveforms would precede abnormal cardiotocography. In the patient reported by Nicolaides *et al.* (1986) cardiotocography and fetal movements were normal in spite of reversed diastolic flow in the umbilical circulation and one of the two fetal deaths reported by Bracero *et al.* (1986) had a reactive non-stress test but an abnormal UA waveform. Seven of our eight pregnancies had non-reactive fetal heart rate patterns at the time abnormal UA waveforms were observed. This is similar to the fetus described by Trudinger *et al.* (1985*a)* which died 5 days after absent diastolic flow and non-reactive cardiotocography were observed. From this limited experience, the temporal relation between non-reactive cardiotocography and abnormal UA waveforms remains unclear (Giles *et al.* 1985*a*; Marx *et al.* 1986) but we may conclude that once the diastolic flow of the umbilical artery circulation is absent or reversed, fetal death is impending and delivery should be considered.

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References

Bracero, L., Schulman, H., Fleischer, A., Farmakides, G. & Rochelson, B. (1986) Umbilical artery velocimetry in diabetes and pregnancy. *Obstet Gynecol* **68,** 654-658.

Erskine, R. L.A. & Ritchie, J. W. K. (1985) Umbilical artery blood flow characteristics in normal and growth-retarded fetuses. *Br J Obstet Gynaecol* **92,** 605-610.

Farmakides, G., Schulman, H., Saldana, L. R., Bracero, L. A., Fleischer, A. & Rochelson, B. (1985) Surveillance of twin pregnancy with umbilical arterial velocimetry. *Am J Obstet Gynecol* **153,** 789-792.

FitzGerald, D. E., Stuart, B. R., Drumm, J. E. & Duignan, N. M. (1984) The assessment of the feto-placental circulation with continuous wave Doppler ultrasound. *Ultrasound Med Biol* **10,** 371-376.

Fleischer, A., Schulman, H., Farmakides, G., Bracero, L., Blattner, P. & Randolph, G. (1985) Umbilical artery velocity waveforms and intrauterine growth retardation. *Am J Obstet Gynecol* **151,** 502-505.

Friedman, D. M., Rutkowski, M., Snyder, J. R., Lustig-Gillman, I. & Young, B. K. (1985) Doppler blood velocity waveforms in the umbilical artery as an indicator of fetal well-being. *J Clin Ultrasound* **13,** 161-165.

Giles, W. B., Trudinger, B. J. & Baird, P. J. (1985*a*) Fetal umbilical artery flow velocity waveforms and placental resistance: pathological correlation. *Br J Obstet Gynaecol* **92,** 31-38.

Giles, W. B., Trudinger, B. J. & Cook, C. M. (1985*b*) Fetal umbilical artery flow velocity-time waveforms in twin pregnancies. *Br J Obstet Gynaecol* **92,** 490-497.

Hsieh, F. J., Chang, F. M., Ko, T. M. & Chen, H. Y. (1987) Percutaneous ultrasound-guided fetal blood sampling in the management of non-immune hydrops fetalis. *Am J Obstet Gynecol* **157,** 44-49.

Huddleston, J. F. & Freeman, R. K. (1977) The use of oxytocin challenge test for the management of pregnancies at risk for uteroplacental insufficiency. In *Perinatal Medicine* (Bolognese, R. J. & Schwanz, R. H., eds), Williams & Wilkins, Baltimore, pp. 68-84.

Marx, G.F., Patel, S., Berman, J. A., Farmakides, G. & Schulman, H. (1986) Umbilical blood flow velocity waveforms in different maternal positions and with epidural analgesia. *Obstet Gynecol* **68,** 61-64.

McCallum, W. D., Williams, C. S., Napel, S. & Daigle, R. E. (1978) Fetal blood velocity waveforms. *Am J Obstet Gynecol* **132,** 425-429.

Nicolaides, K. H., Soothill, P. W., Rodeck, C. H. & Campbell, S. (1986) Ultrasound-guided sampling of umbilical cord and placental blood to assess fetal well-being. *Lancet* **i,** 1065-1067.

Ray, M., Freeman, R., Pine, S. & Hesselgesser, R. (1972) Clinical experience with oxytocin challenge test. *Am J Obstet Gynecol* **114,** 1-9.

Schulman, H., Fleischer, A., Sterm, W., Farmakides, G., Jagani, N. & Blattner, P. (1984) Umbilical velocity wave ratios in human pregnancy. *Am J Obstet Gynecol* **148,** 985-990.

Stuart, B., Drumm, J., FitzGerald, D. E. & Duignan, N. M. (1981) Fetal blood velocity waveforms in uncomplicated labour. *Br J Obstet Gynaecol* **88,** 865-869.

Trudinger, B. J. & Cook, C. M. (1985) Umbilical and uterine artery flow velocity waveforms in pregnancy with major fetal abnormality. *Br J Obstet Gynaecol* **92,** 660-670.

Trudinger, B. J., Giles, W. B., Cook, C. M., Bombardieri, J. & Collins, L. (1985*a*) Fetal umbilical artery flow velocity waveforms and placental resistance: clinical significance. *Br J Obstet Gynaecol* **92,** 23-30.

Trudinger, B. J., Giles, W. B. & Cook, C. M. (1985*b*) Uteroplacental blood flow velocity-time waveforms in normal and complicated pregnancy. *Br J Obstet Gynaecol* **92,** 39-45.

Trudinger, B. J., Giles, W. B. & Cook, C. M. (1985*c*) Flow velocity waveforms in the maternal uteroplacental and fetal umbilical placental circulations. *Am J Obstet Gynecol* **152,** 155-163.

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Kielland's forceps or ventouse—a comparison

YONGYOTH HERABUTYA, PRATAK O-PRASERTSAWAT,
PRASONG BOONRANGSIMANT

Summary. A retrospective study over a 3-year period compared maternal and neonatal outcomes after birth by Kielland's forceps with those by ventouse when there was deep transverse arrest of head. Of the 259 women, 117 were delivered with Kielland's forceps and 142 were delivered with the ventouse. Of the Kielland's forceps deliveries, 15% were performed by a specialist, compared with 41% of the vacuum extractions. There were no differences in maternal morbidity overall, but when groups of operators were compared maternal complications were more frequent in the forceps group with the less experienced operators. There was little early neonatal morbidity (as judged by Apgar score, intubation, admission to the special care baby unit, jaundice and abnormal neurological behaviour) but cephalhaematoma occurred significantly more often in babies born by the ventouse than by Kielland's forceps. There were no perinatal deaths.

The use of mid-cavity rotational forceps has decreased because of their association with maternal injury and poor neonatal outcome (O'Driscoll & Stronge 1975; Chez *et al.* 1980; O'Driscoll *et al.* 1981). Chiswick & James (1979), in a retrospective uncontrolled study, found delayed respiration, birth trauma and abnormal neurological behaviour more frequently in babies born by using Kielland's forceps than in a matched group of babies born spontaneously. The study made no distinction between delivery for fetal distress and delivery for other reasons but when there had been no signs of fetal hypoxia the outcome for babies born by Kielland's forceps was the same as for those born spontaneously. Recently there have been many studies comparing delivery by Kielland's forceps with alternative methods of delivery. Healy *et al.* (1982) were unable to show any difference in neonatal outcome when rotation with Kielland's forceps was compared with manual rotation followed by forceps delivery. Cardozo *et al.* (1983) compared the results of non-rotational forceps, ventouse and emergency caesarean section with Kielland's forceps delivery, and Traub *et al.* (1984) compared the neonatal outcome after emergency caesarean section with that after Kielland's forceps. The outcomes in each study were not significantly different. Vacca *et al.* (1983) and Baerthlein *et al.* (1986) found no significant difference in neonatal outcome between mid-forceps delivery and the ventouse but there was a significant increase in maternal morbidity with mid-forceps delivery.

In Ramathibodi Hospital, the use of Kielland's forceps is still being taught to the obstetrician in training. Kielland's forceps or the ventouse are frequently used in the management of deep transverse arrest of head in the second stage of labour. Many question the wisdom of using forceps when the ventouse would do as

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Department of Obstetrics and Gynecology, Faculty of Medicine, Ramathibodi Hospital, Rama 6 Road, Bangkok 10400, Thailand
YONGYOTH HERABUTYA
PRATAK O-PRASERTSAWAT
PRASONG BOONRANGSIMANT

Correspondence: Y. Herabutya

well if not better. The aim of this study was to compare the outcome of the use of Kielland's forceps with that of ventouse for similar indications at Ramathibodi Hospital between 1982 and 1984.

Patients and methods

The study was performed retrospectively over a 3-year period between 1 January 1982 and 31 December 1984. During this time 19 791 women were delivered in Ramathibodi Hospital and 259 of them were delivered by either Kielland's forceps or by the ventouse because of deep transverse arrest of the head after having been fully dilated and pushing for 30 min in multiparas or 60 min in nulliparas. Those with fetal distress were excluded from the study. Of the 259 women, 117 were delivered by Kielland's forceps and 142 by the ventouse.

Kielland's forceps were applied by attending staff or by third-year residents using a 'wandering' method of application (Parry-Jones 1952). The episiotomy was always made during traction when the perineum was stretched. This was to prevent a possible spiral tear during rotation and to minimize excessive blood loss from early episiotomy (Dewhurst 1981). The ventouse was used by attending staff and by all three levels of residents.

Differences between groups were assessed using the χ^2 test and were regarded as significant at $P<0{\cdot}05$.

Results

The groups did not differ significantly in maternal height or parity. Neither was there any difference in the mean length of first and second stages of labour between the two groups (Table 1).

There were no significant differences in vaginal and cervical lacerations, episiotomy complications, postpartum haemorrhage or blood transfusion. The need for bladder drainage by Foley's catheter was the same in both groups (15%), and the mean hospital stay was also similar (Table 2).

Neonatal outcomes

The mean birthweight of the infants in the Kielland's forceps group was not significantly different from that in the ventouse group (Table

Table 1. Clinical characteristics of the women in two instrumental delivery groups

	Kielland's forceps (n = 117)		Vacuum extractor (n = 142)	
Characteristics	Staff (n = 18)	Resident (n = 99)	Staff (n = 59)	Resident (n = 83)
Primiparas	14 (78%)	72 (73%)	46 (78%)	57 (69%)
Height (cm) Mean (SD)	152·9 (5·35)	152·6 (4·93)	153·5 (4·94)	152·4 (4·69)
Birthweight (g) Mean (SD)	3234·4 (333·3)	3269·9 (346·2)	3216·5 (325·4)	3311·2 (367·8)
Duration of first stage (h) Mean (range)	9·2 (4·7–21·5)	10·2 (4·3–21·1)	10·9 (5·1–25·5)	11·9 (5·0–24·3)
Duration of second stage (min) Mean (range)	52 (38–75)	64 (41–116)	60 (42–93)	64 (40–114)

Table 2. Comparison of maternal morbidity

Variable	Kielland's forceps (n = 117)	Ventouse (n = 142)
Vaginal and cervical laceration	5 (4%)	2 (1%)
Postpartum haemorrhage (>500 ml)	5 (4%)	2 (1%)
Blood transfusion	4 (3%)	1 (1%)
Retention of urine (requiring Foley's catheter)	18 (15%)	21 (15%)
Episiotomy complication	7 (6%)	9 (6%)
Mean length of hospital stay (days)	3·6	3·7

There were no statistically significant differences between the two groups.

1). There was no significant difference in the proportion requiring active resuscitation such as intubation. The Apgar score, admission rate to the special care baby unit, the occurrence of jaundice, abnormal neurological behaviour, neonatal laceration and the mean hospital stay did not differ between the two groups (Table 3). Cephalhaematoma occurred less often in infants born by Kielland's forceps than with the ventouse ($P<0{\cdot}05$). There was no perinatal mortality in either group.

Tables 4 and 5 show the results of attending staff compared with third-year residents. Attending staff used the ventouse more often than the Kielland's forceps but had similar maternal and neonatal results with both instruments. The third-year residents used the Kielland's forceps relatively more frequently but had more maternal complications with the forceps although the neonatal results were similar for both methods.

There were two failed ventouse extractions performed by first- and second-year residents and delivered subsequently by Kielland's forceps and by caesarean section respectively. There were no failures with Kielland's forceps.

Discussion

It has been suggested that the use of Kielland's forceps involves a potential risk to the baby and

Table 3. Early neonatal outcome

Variable	Kielland's forceps (n = 117)	Ventouse (n = 142)
Apgar score		
<5 at 1 min	8 (7%)	8 (6%)
<5 at 5 min	0	0
Intubation	1	1
Immediate admission to special care baby unit	2	1
Late admission to special care for jaundice	11 (9%)	18 (13%)
Seizure	1	1
Facial nerve palsy	2	0
Cephalhaematoma	18 (15%)*	38 (27%)*
Laceration	2 (2%)	4 (3%)
Mean stay in hospital (days)	3·6	4·2
Mortality	0	0

* Cephalhaematoma was less frequent in infants born by Kielland's forceps than by the ventouse ($P<0{\cdot}05$).

Table 4. Comparison of maternal and neonatal complications in Kielland's forceps and vacuum extraction used by attending staff

Instrumental delivery	Number of deliveries	Number of maternal complications	Number of neonatal complications
Kielland's forceps	18/117 (15%)	6/18 (33%)	5/18 (28%)
Vacuum extraction	59/142 (41%)	18/59 (30%)	27/59 (46%)

There were no statistically significant differences between the two methods of instrumental delivery (χ^2-test).

Table 5. Comparison of maternal and neonatal complications in Kielland's forceps and vacuum extraction used by third-year resident

Instrumental delivery	Number of deliveries	Number of maternal complications	Number of neonatal complications
Kielland's forceps	99/117 (85%)	33/99 (33%)	40/99 (40%)
Vacuum extraction	14/142 (10%)	0/14 (—)	6/14 (43%)

There were statistically significantly more maternal complications associated with Kielland's forceps ($P<0{\cdot}05$ χ^2-test).

to the mother (Chalmers 1971; O'Driscoll & Stronge 1975; Chiswick & James 1979, Chez *et al.* 1980; O'Driscoll *et al.* 1981; Gries *et al.* 1981).

We have compared Kielland's forceps delivery with ventouse delivery in the second stage of labour with transverse arrest of head, and found no significant difference in neonatal outcomes. All babies with neurological symptoms initially were normal by the time they were discharged. Chiswick (1980) and Nilsen (1984) found that mid-cavity forceps did not adversely affect the long-term outcome. In our study the only statistically significant difference was that cephalhaematoma occurred more often after the use of ventouse than after Kielland's forceps, but did not affect the occurrence of jaundice which was similar in both groups. Cephalhaematoma is a risk associated with the ventouse particularly when strong traction is exerted in an incorrect direction. There were no significant differences in the maternal outcomes between the two groups.

To investigate the effect of the experience of the operator, we compared the maternal and neonatal complications associated wtih the two methods of instrumental delivery performed by attending staff and by residents. Attending staff had similar complications with both methods but with third-year residents maternal complications were more frequent with Kielland's forceps than with the ventouse, but the neonatal complications were similar with both methods. Our observation of more maternal complications with Kielland's forceps agreed with those of both Vacca *et al.* (1983) and Baerthlein *et al.* (1986). Punnonen *et al.* (1986) found maternal complications to be the same in both groups but their study involved mainly low forceps and only a few mid-forceps deliveries. Deliveries could not be randomly allocated to staff of different experience as this was a retrospective study. Nevertheless, the study suggests that more maternal complications occur when less experienced operators use Kielland's forceps than when they use the vacuum extractor.

In Ramathibodi Hospital the vacuum extractor has become increasingly popular, so much so that when there is a delay in the second stage due to malrotation of the head most obstetricians prefer it to Kielland's forceps. In a retrospective study of clinical practice the random allocation of the instrument to be used was not possible. Thus third-year residents performed a greater proportion of the forceps deliveries than of the vacuum extractions (85% compared with 10%) and the attending staff performed significantly more of the vacuum extractions than of the forceps deliveries (41% compared with 15%). This is because the attending staff believe the ventouse to be less traumatic to both mother and baby. The third-year residents, on the other hand, are taught the use of Kielland's forceps initially and then practise under supervision until they are competent. The residents tend to use the forceps as much as possible to gain experience while supervision is available. The third-year residents, while gaining personal experience with Kielland's forceps, allow more junior residents to use the vacuum extractor for those mid-cavity arrests in which technical difficulty is unlikely.

The conditions under which Kielland's forceps can be applied are the same as those suggested by Paintin (1982); Kielland's forceps should only be used by a trained operator, when the fetal head is deeply engaged in the pelvis and not more than one fifth of fetal head is palpable per abdomen, and in the absence of cephalopelvic disproportion. There were no failed Kielland's forceps deliveries because Kielland's forceps were not applied if more than one fifth of fetal head was palpable per abdomen. On the other hand, there were two failed attempts with the vacuum extractor. One was delivered by Kielland's forceps applied with some difficulty by a member of attending staff. In the other, the head failed to descend with repeated traction, and caesarean section was carried out for suspected cephalopelvic disproportion.

There have been some doubts about the wisdom of continuing to use Kielland's forceps in the modern obstetric practice. In a recent critical review, Richardson *et al.* (1983) found that at the present time much of the published evidence does not support the abandonment of this technique. From the present study it can be concluded that in experienced hands Kielland's forceps cause no more maternal and neonatal complications than the vacuum extractor.

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References

Baerthlein, W. C., Moodley, S. & Stinson, S. K. (1986) Comparison of maternal and neonatal morbidity in mid-forceps delivery and mid-pelvis vacuum extraction. *Obstet Gynecol* **67**, 594-597.

Cardozo, L. D , Gibb, D. M F., Studd, J. W. W. & Cooper, D. J. (1983) Should we abandon Kielland's forceps? *Br Med J* **287**, 315-317.

Chalmers, J A. (1971) *The Ventouse. The Obstetric Vacuum Extractor.* Lloyd-Luke (Medical Books) Ltd, London.

Chez, R. A., Ekbladh, L., Friedman, E. A. & Hughey, M J. (1980) Mid-forceps: is it an anachronism? *Contemp OB/GYN* **15(5)**, 82-100.

Chiswick, M. L. (1980) Forceps delivery—neonatal outcome. In *Outcome of Obstetric Intervention in Britain.* Proceedings of a scientific meeting of the Royal College of Obstetricians and Gynaecologists (Beard, R. W. & Paintin, D. B., eds), RCOG, London, pp. 33-45.

Chiswick, M. L & James, D. K. (1979) Kielland's forceps: association with neonatal morbidity and mortality. *Br Med J* **i**, 7-9.

Dewhurst, J. (1981) *Integrated Obstetrics and Gynaecology for Postgraduates.* 3rd edn, Blackwell Scientific Publications, Oxford, p. 376.

Gries, J. B., Bieniarz, J. & Scommegna, A. (1981) Comparison of maternal and fetal effects of vacuum extraction with forceps on caesarean deliveries. *Obstet Gynecol* **57**, 571-577.

Healy, D. L., Quinn, M. A. & Pepperell, R. J. (1982) Rotational delivery of the fetus: Kielland's forceps and two other methods compared. *Br J Obstet Gynaecol* **89**, 501-506.

Nilsen, S. T. (1984) Boys born by forceps and vacuum extraction examined at 18 years of age. *Acta Obstet Gynecol Scand* **63**, 549-554.

O'Driscoll, K & Stronge, J. M. (1975) Active management of labour in the occipito-posterior position. *Aust NZ J Obstet Gynaecol* **15**, 1-4.

O'Driscoll, K., Meagher, D., MacDonald, D. & Geoghagan, F. (1981) Traumatic intracranial haemorrhage in first born infants and delivery with obstetric forceps. *Br J Obstet Gynaecol* **88**, 577-581.

Paintin, D. B. (1982) Commentary. Mid-cavity forceps delivery. *Br J Obstet Gynaecol* **89**, 495-496.

Parry-Jones, E. (1952) *Kielland's Forceps.* Butterworth, London, p. 67.

Punnonen, R., Aro, P , Kunkankorpi, A. & Pystynen, P. (1986) Fetal and maternal effects of forceps and vacuum extraction. *Br J Obstet Gynaecol* **93**, 1132-1135.

Richardson, D. A., Evans, M. I & Cibils, L. A. (1983) Midforceps delivery: A critical review. *Am J Obstet Gynecol* **145**, 621-632.

Traub, A. I., Morrow, R. J., Ritchie, J. W. K & Dornan, K. J. (1984) A continuing use for Kielland's forceps? *Br J Obstet Gynaecol* **91**, 894-898.

Vacca, A., Grant, A., Watt, G. & Chalmers, I (1983) Portsmouth operative delivery trial: a comparison vacuum extraction and forceps delivery. *Br J Obstet Gynaecol* **90**, 1107-1112.

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Degradation of radiolabelled arginine vasopressin (^{125}I-AVP) by the human placenta perfused *in vitro*

M. J. LANDON, DEBBIE K. COPAS, ELIZABETH A. SHIELLS, J. M. DAVISON

Summary. The capacity of the human placenta to degrade ^{125}I-labelled arginine vasopressin (^{125}I-AVP) was studied *in vitro* using a dual circuit perfused lobule preparation. Seven placentas were perfused with the perfusate on the maternal side of the lobule containing ^{125}I-AVP at the upper limit of the physiological range. On average, over a 30-min period, 48% of the ^{125}I-AVP appeared to have been metabolized. With one exception, a patient whose labour was augmented with intravenous oxytocin, no ^{125}I-AVP apparently crossed the placental lobule to the fetal circulation. These data indicate that the human placenta has a considerable capacity to degrade AVP.

There are marked changes in osmoregulation during normal human pregnancy. Osmotic thresholds for both thirst and the secretion of arginine vasopressin (AVP) decrease, and plasma osmolality and sodium levels both fall significantly (Davison *et al.* 1981, 1984). Despite these changes pregnant women maintain basal levels of plasma AVP similar to non-pregnant values of 1 to 2 pg/ml and can concentrate their urine appropriately when they are dehydrated. This is surprising because the metabolic clearance rate of AVP rises three- to four-fold during pregnancy (Davison *et al.* 1987). The increased metabolic clearance rate may be a consequence of high serum vasopressinase levels, destruction *in situ* by the placenta, or other unidentified changes in AVP metabolism in pregnancy. The placenta is known to produce cystine aminopeptidase, a potent vasopressinase which circulates at levels capable of destroying nanogram quantities of AVP per minute *in vitro* (Tuppy 1968; Rosenbloom *et al.* 1975). In the present study the capacity of the placenta itself to degrade radiolabelled AVP was tested in an in-vitro perfusion system.

Patients and methods

Placentas from seven patients were studied. All had had normal full term pregnancies with no obstetric or medical problems. With one exception (no. 5) labour and delivery were uneventful. Clinical details of the patients studied are given in Table 1.

Placental perfusion

Placentas were collected as they were delivered and a single lobule was perfused as described by Penfold *et al.* (1981). After the fetal artery and vein supplying a lobule had been cannulated and cleared of blood, the 'maternal circulation' was established by passing two fine glass cannulae

Section of Perinatal and Child Health, Clinical Research Centre, Watford Road, Harrow, Middlesex HA1 3UJ
M. J. LANDON
DEBBIE K. COPAS

MRC Human Reproduction Group, Princess Mary Maternity Hospital, Great North Road, Newcastle-upon-Tyne NE2 3BD
ELIZABETH A. SHIELLS
J. M. DAVISON

Correspondence: M. J. Landon

Table 1. Clinical details

	Patient number						
	1	2	3	4	5	6	7
Age (years)	22	30	42	38	32	27	28
Parity	0	0	3	2+2	2+1	0+1	1
Gestation (weeks)	41	40	40	39	40	38	42
Induced labour	Yes	No	No	No	No	No	No
Onset (induction)–delivery interval (h)	7·2	14·5	8·25	3·2	15·5	9·1	4·3
Delivery	NVD	Forceps	NVD	NVD	LSCS	NVD	NVD
Birthweight (kg)	3·48	2·96	3·47	3·93	2·44	3·12	3·57
Sex of infant	F	F	M	F	M	M	M

NVD, Normal vaginal delivery; LSCS, lower segment caesarean section.

into the intervillous space. Both sides of the lobule were perfused with a Krebs-Ringer bicarbonate buffer solution containing 0·84% dextran (av. mol. wt 17 900) gassed with 95% oxygen: 5% carbon dioxide but the maternal perfusate also contained creatinine (200 μg/ml) as an internal standard of diffusional permeability. The 'maternal' inflow rates varied between 13·4 ml/min and 14·0 ml/min but the fetal inflow was a constant 7·0 ml/min. Outflow rates were always within 0·1 ml/min of the corresponding inflow rate. The pH of both maternal and fetal inflows was checked periodically and found to be between 7·35 and 7·46. The placenta and perfusion fluids were maintained throughout at 37°C in a thermostatically controlled cabinet. Perfusion fluids were *not* re-circulated.

After an initial 30-min perfusion period to allow the preparation to reach a steady state, ^{125}I-AVP, labelled by the chloramine T method to a specific activity between 480 μCi and 726 μCi per μg AVP, was added to the maternal perfusate to a concentration of about 5 pg/ml. This is at the upper limit of the physiological range but was necessary to achieve reasonable counting rates during subsequent analytical procedures. Labelled AVP was perfused for a further 30 min and a 5-min sample of both fetal and maternal outflows was collected at the beginning and the end of this period. To inhibit any cystine aminopeptidase in the outflow samples these samples were collected into *o*-phenanthroline (freshly prepared solution 60 mg/ml: 100 μl per 10 ml sample, 1:10 phenanthroline monohydrate, BDH Chemicals Ltd, Poole, UK). They were immediately centrifuged at 1000 *g* for 5 min and the supernatant stored frozen for analysis within 5 days.

Analytical methods

Outflow samples were counted for total ^{125}I content and the percentage of labelled fragments determined by gel chromatography. A maternal outflow sample (0·5 ml) or a fetal outflow sample (1·0 ml) were applied to a 10 mm × 400 mm column of Sephadex G-25 (superfine) and eluted at room temperature with 0·2 M acetic acid containing 0·2 mg/ml sodium azide as preservative. The flow rate was 5 ml/h and 80 × 0·5 ml fractions were collected. The radioactivity of the fractions was measured and the counts per fraction plotted against elution volume. Authentic ^{125}I-AVP was treated similarly and the peak of intact AVP identified by comparison. The percentage of intact AVP was calculated from the area under the elution profile.

At the end of each experiment the perfused lobule was excised and weighed. It was homogenized in an equal volume of 0·2 M acetic acid using a Silverson blender. The homogenate was centrifuged at 1000 *g* for 15 min, samples of both supernatant and residue were counted, and an aliquot of the supernatant was analysed by chromatography as described above.

Creatinine was measured by the alkaline picrate method (Jaffe reaction) using a commercial reagent kit (No. 555A, Sigma Chemical Company).

Results

The results of these perfusions are detailed in Table 2. The total recovery of ^{125}I itself ranged from 83% to 105% (mean 95%) with 72% to 92% (mean 82%) recovered in the maternal outflow, 2% to 11% (mean 5%) in the fetal outflow

Table 2. Results from perfusion experiments

	Patient number							
Variable	1	2	3	4	5	6	7	Mean
Perfused lobule								
Creatinine clearance (ml/min)	0·35	0·36	0·51	1·10	0·47	0·84	0·48	0·59
Maternal perfusion rate (ml/min)	13·4	13·6	14·0	14·0	13·8	13·8	13·8	13·8
Lobule weight (g)	24	25	19	24	38	30	21	26
Placental weight (g)	590	600	690	640	410	520	500	564
Total recovery of ^{125}I as a percentage of perfused ^{125}I-AVP								
Placental lobule	4	6	4	10	10	14	7	8
Fetal outflow	2	3	5	6	5	11	4	5
Maternal outflow	79	87	92	80	81	80	72	82
Recovery of intact ^{125}I-AVP as a percentage of perfused ^{125}I-AVP								
Placental lobule	2·0	2·5	0·5	3·0	0·5	0·9	0·2	1·4
Fetal outflow	0	0	0	0	0·2	0	0	
Maternal outflow	32	34	64	49	68	58	58	52
Calculated loss of AVP from buffer during perfusion through the maternal side of the lobule								
'Clearance' of maternal inflow (ml/min)	9·1	8·9	5·0	7·1	4·4	5·8	5·8	6·6
AVP removed by lobule (ng/min)	0·055	0·038	0·031	0·061	0·023	0·029	0·054	0·042
As percentage of supply	68	66	36	51	32	42	42	48

and 4% to 14% (mean 8%) remaining in the excised lobule at the end of the experiment.

Chromatography on Sephadex G-25 showed that the recovery of apparently intact AVP ranged from 32% to 68% (mean 52%) on the maternal side, was not detectable at all on the fetal side of six of the seven placentas studied, and the lobule itself contained up to 3% of the perfused AVP load (some of the radioactivity remaining in the lobule could not be extracted with either buffer or Triton X-100 so its identity remains unknown).

This means that the maternal perfusate 'lost' on average 48% of its AVP content as a result of perfusion through the intervillous space on the maternal side of the placenta. Expressing these data as the volume of maternal perfusate totally cleared of AVP during perfusion gives 'clearances' ranging from 4·4 to 9·1 (mean 6·6) ml/min.

Using data on counting efficiency and the specific activity of the labelled AVP perfused, absolute rates of breakdown per lobule could be calculated, these ranged from 0·023 ng/min to 0·061 ng/min (mean 0·042 ng/min).

The diffusional clearance for creatinine averaged 0·6 ml/min in the same series of placentas.

Discussion

Clearly the *in vitro* perfused lobule has an appreciable capacity for the catabolism of ^{125}I-AVP, but the precise in-vivo implications are difficult to calculate. If a lobule weighing on average 26 g can 'clear' nearly 7 ml/min then *pro rata* the whole placenta (average weight 564 g) would clear some 150 ml/min: about 30% of some estimates of uteroplacental blood flow (Faber & Thornburg 1983). Similarly, if on average the lobule can destroy 0·042 ng/min then by the same calculation the whole placenta could destroy nearly 1 ng of AVP/min which at normal AVP blood levels of 1 pg/ml gives a potential clearance by the whole placenta approaching 1000 ml/min—more than twice the same estimates of uteroplacental blood flow.

These calculations can only be broad approximations because of inherent imprecisions in defining the mass of placental tissue involved during lobule perfusion. The weight of the lobule may not be an accurate measure of the biochemically active mass and the whole placenta is unlikely to have an even distribution of either enzyme activity or blood flow.

Furthermore the 'maternal circulation' depends largely on the position of the two cannulae within the intervillous space and shunting within this space could determine how effectively the placental tissue is exposed to the perfusing solution. The rate of metabolism is likely to be reduced if diffusion plays a significant role in the distribution of substrate within the lobule. The diffusional clearance of creatinine from maternal to fetal circulation gives some measure of the matching of the two circulations and would be expected to signal any changes in flow pattern but it will not reflect biochemically active mass. Nor is the distribution of AVP or its metabolites necessarily restricted entirely to the apparent lobule. Lateral diffusion into adjacent tissue is possible and these losses cannot readily be measured or included in the final analysis.

Given these uncertainties it is perhaps not surprising that there was a four-fold range in the apparent capacity of the lobules to catabolize ^{125}I-AVP which was not related to lobule weight or creatinine clearance and that there was some variation in the percentage of ^{125}I finally recovered.

A significant amount of ^{125}I was retained by the lobule at the end of the experiment and some at least appeared to be intact AVP. Given the rapidity with which cystine aminopeptidase can destroy AVP *in vitro* (Rosenbloom *et al.* 1975), it is surprising that any intact AVP remained within the placenta. This may be a reflection of the complexity of AVP breakdown. Recent studies on brain tissue suggest that the catabolism of AVP involves a series of reactions producing a number of intermediate peptides (Burbach & Lebouille 1983). The relatively simple analytical technique used in these studies may not distinguish intact AVP from the initial reaction products and if this is so then this preliminary analysis is certain to underestimate the extent to which AVP itself has been inactivated.

Whatever the interpretation, the failure to wash out all the ^{125}I from the lobule either with a buffer or more aggressive methods suggests that a proportion of the label at least is tightly bound to placental tissue. AVP receptors have been described in other tissues (Guillon *et al.* 1982; Berrettini *et al.* 1982; Kim *et al.* 1985) and their presence within the placenta cannot be excluded. Binding may precede metabolism and both could be sensitive to the rate of AVP supply. The perfused levels of AVP were at upper physiological limits (Davison *et al.* 1984), but this had no apparent effect on the perfused lobule. There were no measurable changes in flow, pressure or creatinine clearance as a result of adding AVP to the buffer perfusing the maternal intervillous space and there was no evidence that outflow samples collected at the beginning of perfusion contained more or less AVP than those collected at the end. It may be significant, however, that the one patient (no. 5) who had a prolonged labour (15·5 h), with intravenous infusion of oxytocin (Syntocinon) for 6 h before a caesarean section, had the lowest lobule clearance in the series. Furthermore, this was the smallest placenta in the series and the only case in which any AVP appeared to have crossed to the fetal circulation intact. Perhaps the above average amount of oxytocin infused during labour saturated the receptor(s) or enzyme system(s) involved and inhibited AVP metabolism during subsequent in-vitro perfusion. There is some evidence that under similar circumstances oxytocin crosses to the fetus (Buchan 1979).

It seems likely that in the absence of maternal intravenous oxytocin during labour and delivery the placenta effectively protects the fetus from the vagaries of maternal AVP physiology. There is, however, evidence that the fetus responds to the degree of maternal hydration and part of this response is a change in fetal AVP levels (Leung *et al.* 1980; Ervin *et al.* 1986). Analysis of paired artery and vein samples of cord blood shows a significant loss of AVP after circulation through the fetal side of the placenta. Assuming an umbilical blood flow rate of 300 ml/min, the data of Johannesen *et al.* (1985) give a calculated AVP loss of approximately 1·5 ng/min, not dissimilar to the average value calculated for the maternal side in the present series, although earlier studies (Leung *et al.* 1980) suggested that the loss might be somewhat greater.

There are few data on the kinetics of AVP degradation by cystine aminopeptidase, the enzyme generally held to be responsible. The quoted K_m value of $1{\cdot}07 \times 10^{-5}$ M (Tuppy 1968) far exceeds the levels of AVP involved in these experiments nor is it known whether oxytocin, as suggested by results in patient no. 5, would be an effective competitor. There is some evidence that the oxytocin molecule is more robust than that of AVP (Burbach *et al.* 1982) and this is supported by data showing that the metabolic clearance rate of oxytocin during pregnancy, unlike that of AVP, is essentially unchanged (Amico *et al.* 1987).

In conclusion: during in-vitro perfusion of the maternal intervillous space nearly 50% of ^{125}I-AVP was destroyed. That the AVP was not totally destroyed could reflect the complexity of the breakdown process, shunting within the intervillous space or an overestimate of the AVP recovered. Nevertheless, the human placenta clearly has a capacity to inactivate AVP at plasma levels considerably in excess of those usually found physiologically. Whether this capacity extends to or is influenced by the metabolism of oxytocin or other synthetic peptides such as 1-desamino-8-D-arginine vasopressin (DDAVP) and the clinical implications remain to be established.

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References

Amico, J. A., Ulbrecht, J. S. & Robinson, A. G. (1987) Clearance studies of oxytocin in humans using radioimmunassay measurements of the hormone in plasma and urine. *J Clin Endocrinol Metab* **64**, 340-345.

Berrettini, W. H., Post, R. M., Worthington E. K. & Casper, J. B. (1982) Human platelet vasopressin receptors. *Life Sci* **30**, 425-432.

Buchan, P. C. (1979) Pathogenesis of neonatal hyperbilirubinaemia after inductioi of labour with oxytocin. *Br Med J* **ii**, 1255-1257.

Burbach, J. P. H., Wang, X. & Ittersum, M. (1982) Difference in susceptibility of arginine-vasopressin and oxytocin to aminopeptidase activity of brain synaptic membranes. *Biochem Biophys Res Commun* **108**, 1165-1171.

Burbach, J. P. H. & Lebouille, J L. M (1983) Proteolytic conversion of arginine-vasopressin and oxytocin by brain synaptic membranes. *J Biol Chem* **258**, 1487-1494.

Davison, J. M., Vallotton, M. B. & Lindheimer, M. D. (1981) Plasma osmolality and urinary concentration and dilution during and after pregnancy: evidence that lateral recumbency inhibits maximal urinary concentrating ability. *Br J Obstet Gynaecol* **88**, 427-479.

Davison, J. M., Gilmore, E. A., Dürr, J., Robertson, G L & Lindheimer, M. D. (1984) Altered osmotic thresholds for vasopressin secretion and thirst in human pregnancy. *Am J Physiol* **246**, F105-F109

Davison, J. M., Shiells, E. A., Philips, P. R., Barron, W. M. & Lindheimer, M. D. (1987) Metabolic clearance rates (MCR) of vasopressin (AVP) increase markedly in gestation: a possible cause of polyuria in pregnant women *Clin Res* **35**, 646A.

Ervin, M G., Ross, M. G., Youssef, A., Leake, R. D. & Fisher, D. A. (1986) Renal effects of ovine fetal arginine vasopressin secretion in response to maternal hyperosmolality. *Am J Obstet Gynecol* **155**, 1341-1347.

Faber, J. J. & Thornburg, K. L. (1983) *Placental Physiology*. Raven Press, New York, pp. 33-54.

Guillon, G., Butlen, O., Cantau, B., Barth, T. & Jard, S. (1982) Kinetic and pharmacological characterization of vasopressin membrane receptors from human kidney medulla: relation to adenylate cyclase activation. *Eur J Pharmacol* **85**, 291-304.

Johannesen, P., Pederson, E. B. & Rasmussen, A. B. (1985) Arginine vasopressin in amniotic fluid, arterial and venous cord plasma and maternal venous plasma. *Gynecol Obstet Invest* **19**, 192-195.

Kim, J. K., Dillinghan, M. A., Summer, S. N., Ishikawa, S., Anderson, R. J. & Schrier, R. W. (1985) Effects of vasopressin antagonists on vasopressin binding, adenylate cyclase activation and water flux. *J Clin Invest* **76**, 1530-1535.

Leung, A. K. C., McArthur, R. G., McMillan, D. D., Ko, D , Deacon, J. S. R , Parboosingh, J. T. & Lederis, K P. (1980) Circulating antidiuretic hormone during labour and in the newborn. *Acta Paediatr Scand* **69**, 505-510.

Penfold, P., Drury, L., Simmonds, R. & Hytten, F E. (1981) Studies of a single placental cotyledon *in vitro:* I. The preparation and its viability. *Placenta* **2**, 149-154.

Rosenbloom, A. A., Sack, J & Fisher, D. A. (1975) The circulating vasopressinase of pregnancy: species comparison with radioimmunoassay. *Am J Obstet Gynecol* **121**, 316-320.

Tuppy, H. (1968) The influence of enzymes on neurohypophysial hormones. In *Handbuch der Experimentellen Pharmakologie: Neurohypophyseal Hormones and Similar Peptides*. Springer-Verlag, Berlin. **28**, 67-129.

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Helminth infestations in Asian women attending an antenatal clinic in England

G. CONSTANTINE, L. ARUNDELL, K. FINN, P. LOWE,
A. O'CONNOR, D. M. LUESLEY

Summary. Asian women attending an antenatal clinic in England were studied to determine the infestation rates with intestinal helminths. An overall rate of 9% was found, rising to 18% in those women resident for less than 7 years. Indians had a carriage rate of 3%, Pakistanis 7·3% and Bangladeshis 45%. Species detected were hookworm, whipworm (*Trichuris trichiura*), dwarf tapeworm (*Hymenolepis nana*) and roundworm (*Ascaris lumbricoides*).

Intestinal infestations are a common finding amongst pregnant women in Third World countries. Often these appear to be asymptomatic, although in these areas hookworm is a common cause of anaemia in pregnancy. Such infestations are rare amongst the indigenous population of the UK but during the past 30 years many young Asian women have come to live in this country, and they may make frequent prolonged trips back to their country of origin.

Following a maternal death from disseminated strongyloidiasis (Smallman *et al.* 1986), and a case of amoebic peritonitis in pregnancy (Constantine *et al.* 1987), we decided to investigate the prevalence of intestinal infestations amongst the Asian women in the antenatal clinic at Dudley Road Hospital, Birmingham. This was combined with a survey of the duration of residence in the UK of the Asian antenatal population, and the frequency and duration of trips back to their country of origin.

Patients and methods

Overall 337 Asian women attending the antenatal clinic were asked to fill in a questionnaire, if necessary through an interpreter. The method employed was to approach all Asian women attending specific clinics. The questionnaire provided information about country of origin and length of residence in the UK. Of these 337 women 187 were from India, 105 from Pakistan and 45 from Bangladesh. Data on the date and length of their last visit home were available for 320 women. A control group of 94 white women was also studied. Each woman was asked to provide a fresh stool sample at her next clinic visit. It was felt that for the purposes of this study to ask for more than one sample from each woman would make compliance very poor, and was not necessary (Thompson *et al.* 1972). Of the 196 women who provided samples 101 were from India (mean age 25, SD 5·5 years; 38% primiparous), 55 were from Pakistan (mean age 29·7, SD 6·6 years; 18% primiparous), 22 were from Bangladesh (mean age 28·4, SD 9·6 years; 14% primiparous) and 18 were white (mean age 24·5, SD 7·9 years; 40% primiparous), giving compliance rates of 54%, 52%, 49%, and 19% respectively.

Dudley Road Hospital, Dudley Road, Birmingham B18 7QH
Department of Obstetrics and Gynaecology
G. CONSTANTINE *Senior Registrar*
L. ARUNDELL *Medical Student*
K. FINN *Registrar*
A. O'CONNOR *SCM SRN*
D. M. LUESLEY *Senior Lecturer*

Department of Medical Microbiology
P. LOWE *Chief MLSO*

Correspondence: Dr G. Constantine

The samples were examined by two methods:

Direct wet preparation. A smear of the stool specimen in saline was examined microscopically, using 1:10 iodine to stain for *Strongyloides*.

Concentration method. The stool specimens were fixed and sterilized in formalin and saline for 30 min. The resulting suspension was then passed through a coarse filter, and the filtrate was treated with ether to remove fats. The product was spun at 1000 r/min for 10 min, and the sediment was examined microscopically for parasite ova.

Whilst some parasites, such as *Entamoeba histolytica*, cannot be reliably detected by these methods, they are suitable for detecting common helminths such as hookworm (*Ancylostoma duodenale, Necator americanus*), whipworm (*Trichuris trichiura*), *Strongyloides stercoralis*, dwarf tapeworm (*Hymenolepis nana*) and roundworm (*Ascaris lumbricoides*).

Results

Table 1 details the results, subdivided by country of origin and species of parasite. A total of 17 women returned positive samples, two women had dual infestations. Hookworm and dwarf tapeworm predominated in women from India and Pakistan, whilst whipworm and roundworm were found in women from Bangladesh. When expressed as a percentage of all samples returned, Indians had a carriage rate of 3%, Pakistanis 7% and Bangladeshis 45%. There were no positive samples returned by white women, but the compliance with return of samples was very poor in this group. The difference in carriage rates between the Bangladeshis and the Indians, Pakistanis and whites was highly significant ($P<0{\cdot}001$). The differences between the other populations were not statistically significant.

All women who returned positive samples had been resident in the UK for less than 7 years; four for less than 1 year, whilst six had been resident for over 4 years, none having returned home. Although the overall carriage rate for Asians was 9·5%, it rose to 18% in those women resident for less than 7 years. Of the Asian women questioned 51% had been in the UK for less than 7 years. Significantly more Bangladeshis had been in this country for less than 7 years than either Indians ($P = 0{\cdot}001$) or Pakistanis ($P = 0{\cdot}01$).

Of the 320 Asians answering the question, 200 had never returned to their country of origin. Of the remaining 120, 50 (42%) had returned in the last 2 years, and 91 (76%) within the last 5 years.

Combining the above data, 191 Asian women (60%) had either been resident in, or returned to, their country of origin within the previous 5 years.

Discussion

There are few data available on the prevalence of intestinal parasites in ethnic groups in the UK. The incidence of such parasites in 4000 immigrant children was studied between 1968 and 1970 (Thompson *et al.* 1972). Asian children had carriage rates of 30–40%, hookworm, dwarf tapeworm, whipworm and roundworm predominating. One recent study of this problem in pregnancy has been published (D'Alauro *et al.* 1985). Of 147 women in a refugee camp in Thailand 54% were found to be carriers of parasites, hookworm and *Giardia lamblia* being the most prevalent. This population is unlikely, however, to be representative of any group in the UK.

Our data highlight the surprisingly high overall carriage rate of intestinal helminths in the Birmingham Asian population (9·5%). When women resident in the UK for less than 7 years

Table 1. Infestation of Asian subjects

Country of origin	Total tested	Hookworm	Whipworm	Roundworm	Dwarf tapeworm	Total positive *n* (%)
India	101	3	0	0	1	3* (3)
Pakistan	55	3	0	0	1	4 (7)
Bangladesh	22	0	9	2	0	10* (45)
Total	178	6	9	2	2	17 (9)

*Includes one woman in each group with a dual infestation.

are considered, the overall carriage rate increases to 18%. Much of this is concentrated in the Bangladeshi population (45%), who have a significantly higher carriage rate than other groups ($P = 0{\cdot}001$). We believe that this may be explained by the fact that the pattern of immigration from Bangladesh is different to that from India and Pakistan. Bangladeshis appear to be from a more rural background, living in closer proximity to water and in conditions favourable to the life-cycle of these helminths.

Interestingly, the Bangladeshi women attending our clinic had been in the UK for significantly shorter periods than the Indians and Pakistanis, suggesting changing patterns of immigration. Despite this, however, 5 of the 10 Bangladeshi women with infestations had been in the UK, without returning home, for 4 or more years. It would thus appear that on both counts Bangladeshis are a particularly 'at risk' group.

The helminths that we detected in our study, i.e. hookworm, whipworm, roundworm and dwarf tapeworm, are usually asymptomatic and cause little morbidity. Often therefore no treatment is required during pregnancy (D'Alauro *et al.* 1985; Ellis 1986; McGregor *et al.* 1983). All can, however, become symptomatic in favourable circumstances, or if the worm load increases. Gastrointestinal symptoms predominate, although anaemia is a well-known finding in patients with heavy hookworm infestations.

Strongyloides stercoralis and dwarf tapeworm differ from other species in that both can give rise to a fulminating invasive hyperinfection state (Smallman *et al.* 1986). Host immune response normally prevents this by limiting the quantity of infective larvae produced in the gut and inhibiting successful penetration of larval forms. Increases in parasite burden may occur when the immunological state of the host changes (as in pregnancy), allowing an increase in parasite numbers, and larvae from the gut to invade. Despite this, the combination of intestinal infestation and pregnancy is extremely common throughout much of the world, and only rarely gives rise to problems.

All helminths normally undergo part of their life-cycle outside the host, e.g. in soil. Because of this it is often assumed that an infestation will die out if the environmental circumstances are unsuitable. The life span of a roundworm is estimated at 1 year, and hookworm 3–15 years depending on the species (Weatherall *et al.* 1985). *Strongyloides stercoralis* can remain quiescent for many years (Gill & Bell 1980) and like hookworm and dwarf tapeworm can complete its life-cycle in the human gastrointestinal tract. Internal autoinfection may thus occur (Beaver *et al.* 1984). Our study confirms that infestations with hookworm, dwarf tapeworm and whipworm can persist for at least 6 years after leaving an endemic area. One woman also carried roundworm 6 years after her last contact with Bangladesh.

We have shown helminth infestations to be common in our Asian antenatal clinic population, particularly the Bangladeshis, and quantified this. Routine screening and treatment in pregnancy is probably not worthwhile. The occasional serious potential morbidity/mortality associated with intestinal infestations in pregnancy should, however, be borne in mind, and symptomatic women should be investigated. If parasites are found, treatment is safe, simple and effective and should not be withheld. The possibility of other imported diseases in Asian immigrants attending antenatal clinics should be noted. This applies both to recent immigrants and also those returning to their country of origin for prolonged visits.

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References

Beaver, D C., Jung, R C. & Cupp, E. W. (1984) *Clinical Parasitology*. Lea & Febiger, Philadelphia, pp. 253-268, 509-511.

Constantine, G., Menon, V & Luesley, D. (1987) Amoebic peritonitis in pregnancy in the United Kingdom. *Postgrad Med J* **63**, 495-496

D'Alauro, F., Lee, R. V., Pao-in, K. & Khairallah, M. (1985) Intestinal parasites and pregnancy. *Obstet Gynecol* **66**, 639-643.

Ellis, C J. (1986) Antiparasitic agents in pregnancy *Clin Obstet Gynaecol* **13**, 269-275.

Gill, G V. & Bell, D. R. (1980) Persisting tropical diseases amongst former prisoners of war of the Japanese *Practitioner* **224**, 801-804.

McGregor, J. A., Wall, R. E. & LaForce, F. M. (1983) Infectious diseases; parasitic infestations. In

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Suspected ectopic pregnancy: ultrasound findings and hCG levels assessed by an immunofluorometric assay

BRUNO CACCIATORE, PEKKA YLÖSTALO,
ULF-HÅKAN STENMAN, OLOF WIDHOLM

Summary. One hundred suspected ectopic pregnancies were assessed by ultrasound on the basis of the following criteria: (A) viable intrauterine fetus, intrauterine pregnancy is certain; (B) intrauterine double sac or eccentric ring, intrauterine pregnancy is probable; (C) empty uterus or central ring but no adnexal mass or cul-de-sac fluid, ectopic pregnancy is possible; (D) empty uterus or central ring and an adnexal mass or cul-de-sac fluid, ectopic pregnancy is probable; (E) viable ectopic fetus, ectopic pregnancy is certain. Serum human chorionic gonadotrophin (S-hCG) was detected by an immunofluorometric assay (sensitivity 0·2 i.u./l, cut-off level 10 i.u./l). All the 51 patients in groups A and B had an intrauterine pregnancy. Normal gestational sacs were found also at S-hCG levels of <3600 i.u./l, the lowest level being 894 i.u./l. Ectopic pregnancy was confirmed in 29 of the 30 women in groups D and E. In the 19 women categorized into group C serial hCG assay and repeated sonography diagnosed ectopic pregnancy in 12 and miscarriage of an intrauterine pregnancy in the other seven. Ectopic pregnancy was always found when no gestational sac was seen by sonography and the hCG level was >1000 i.u./l.

The combined use of ultrasound and highly sensitive assays for human chorionic gonadotrophin (hCG) has improved the diagnosis of ectopic pregnancy (Weckstein 1985; Weckstein *et al.* 1985; Batzer & Corson 1986). Radioimmunoassays (RIA) for hCG are extremely accurate in confirming or ruling out the presence of growing trophoblastic tissue (Seppälä *et al* 1981) and an abnormal pregnancy is strongly suspected if the hCG level does not double in 2–3 days. However, in about 10% of ectopic pregnancies serum hCG shows a normal rate of increase (Romero *et al.* 1986).

Early localization of the pregnancy still remains a clinical challenge. Sonographic demonstration of fetal echoes within the fallopian tubes is rare (Laing & Jeffrey 1983) and the assessment of adnexal masses is still controversial. Therefore ultrasound is used to exclude ectopic pregnancy by identifying a normal intrauterine pregnancy. Lack of evidence for an intrauterine sac by sonography in combination with an hCG level above 6000–6500 mi.u./ml (1st International Reference Preparation) strongly suggest ectopic pregnancy (Kadar *et al.* 1981; Romero *et al.* 1985*a*). However, this condition is rare, and most ectopic pregnancies have lower hCG concentrations (Cartwright & Di Pietro 1984). Furthermore the occurrence of a

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II Department of Obstetrics and Gynaecology,
Helsinki University Central Hospital,
Haartmaninkatu 2, SF-00290 Helsinki, Finland
BRUNO CACCIATORE
PEKKA YLOSTALO
ULF-HÅKAN STENMAN
OLOF WIDHOLM

Correspondence: Pekka Ylöstalo

pseudogestational sac observed in up to 20% of ectopic pregnancies may confuse the sonographic identification of an early gestational sac (Marks *et al.* 1979; Wexler *et al.* 1984).

In this study sonography in combination with hCG levels, assayed by highly sensitive immunofluorometric assay (IFMA), was used in the assessment of suspected ectopic pregnancy. Sonographic findings were categorized into five groups and the usefulness of these criteria as guidelines for follow-up and treatment was studied.

Subjects and methods

One hundred women suspected of having an ectopic pregnancy were referred for ultrasonography on the basis of a positive pregnancy test and abdominal pain. The study was approved by the ethics committee of the hospital.

Serum hCG concentrations were determined by an immunofluorometric assay (DELFIA), with a sensitivity of 0·2 i.u./l calibrated against the 2nd International Standard (2nd IS) and a cut-off level of 10 i.u./l (Stenman *et al.* 1983).

Sonography was performed with real-time sector scanners (Aloka SSD 710 and 280 SL) with 3·0 and 3·5 MHz transducers. A full bladder was required. Particular attention was paid to examination of the uterine content. The double sac sign and the topography of the sac were identified according to Bradley *et al.* (1982) and Abramovici *et al.* (1983). The uterus was classified as empty if only endometrial echoes were seen. The ovaries were identified as described by Campbell *et al.* (1983). The presence of cystic adnexal masses, separated from the ovaries, was considered highly indicative of ectopic pregnancy (Coleman *et al.* 1985). According to the result of the first ultrasound examination the women were assigned to one of the following five groups.

Group A A living intrauterine fetus was seen.

Group B. An intrauterine double sac or an eccentric ring or both were seen. Intrauterine pregnancy was considered probable, hCG assay and ultrasound scan were performed after 1 week.

Group C. The uterus was empty or a central ring was seen but no adnexal masses or cul-de-sac fluid were found Ectopic pregnancy was considered possible, hCG assay and ultrasound scan or laparoscopy were performed within a week.

Group D. The uterus was empty or a central ring was seen and an adnexal mass or cul-de-sac fluid was found. Ectopic pregnancy was considered probable and laparoscopy or laparotomy were performed.

Group E. A viable ectopic fetus was detected; laparotomy was performed.

The intrauterine pregnancies were classified as normal if the scan revealed a viable intrauterine fetus and as abnormal if a miscarriage was diagnosed histologically after curettage. The presence of an ectopic pregnancy was confirmed by histological examination of tissue samples obtained during surgery.

Results

Ectopic pregnancy was histologically proven in 41 patients and tubal rupture occurred in seven women. In the other 59 women an intrauterine pregnancy was found. The clinical outcome was normal in 36 women and 23 had a miscarriage.

Table 1. Correlation of the ultrasound finding on admission with clinical outcome in 100 suspected ectopic pregnancies

		Clinical outcome		
			Intrauterine pregnancy	
Ultrasound findings	No. of women	Ectopic pregnancy	Normal	Abnormal
(A) Viable intrauterine fetus	6	0	6	0
(B) Double sac or eccentric ring	45	0	30	15
(C) No sac or central ring, no mass	19	12	0	7
(D) No sac or central ring, adnexal mass	26	25	0	1
(E) Viable ectopic fetus	4	4	0	0
Total	100	41	36	23

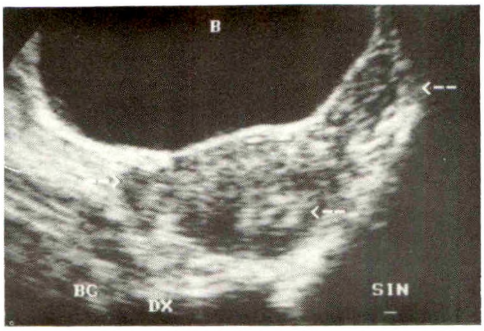

Fig. 1. Sonograph showing a double sac, eccentrically located in the uterine cavity (arrowhead) and ovaries (arrowheads on the left and on the right). B, Bladder; DX, right side; SIN, left side; BC, operator.

The ultrasound findings in relation to the clinical outcome are summarized in Table 1. All six patients in group A had a normal pregnancy. Of the 45 women classified as group B, an intrauterine double sac was seen in 39 (Fig. 1) and an eccentric transsonic ring, ranging in diameter from 4 to 8 mm, but no double sac, in the other six who all had hCG concentrations <3600 i.u./l, the lowest being 894 i.u./l. Three of these pregnancies had a normal outcome whereas the other three miscarried (Fig. 2).

Of the 59 intrauterine pregnancies 51 (86%) were detected by the ultrasound criteria used for groups A and B. There were no false positives.

Ectopic pregnancy was suspected by sonography in 49 women categorized as groups C, D and E. In four pregnancies sonography detected a viable ectopic fetus (group E) and this was confirmed by laparotomy. In the 26 women in group D adnexal masses were detected. They were cystic with a thick echogenic contour in 15 women (Fig. 3) of whom 14 had an unruptured ectopic sac and one a ruptured sac. In the 11 other women a mass with a more complex structure was found (Fig. 4). Cul-de-sac fluid was detected in six echograms. Laparoscopy confirmed ectopic pregnancy in all except one of the 26 women. This woman had thick adhesions in the cul-de-sac and miscarriage was diagnosed by curettage.

None of the 41 women with ectopic pregnancy had an intrauterine double sac or eccentric ring detected by sonography. A pseudogestational sac was found in 12 (29%) of these and it always appeared as an irregular centrally located ring. In 22 women thick endometrial echoes were detected and in seven others a thin linear endometrial echopattern was found.

None of the 19 women in group C had an adnexal mass or cul-de-sac fluid detected by ultrasound on admission. On the basis of the clinical findings and an hCG level >2500 i.u./l three women were laparoscoped immediately and an ectopic pregnancy was detected. In 15 patients serial assessment of hCG levels and further ultrasound scan was performed within a week. An adnexal mass was detected in eight women and ectopic pregnancy was confirmed

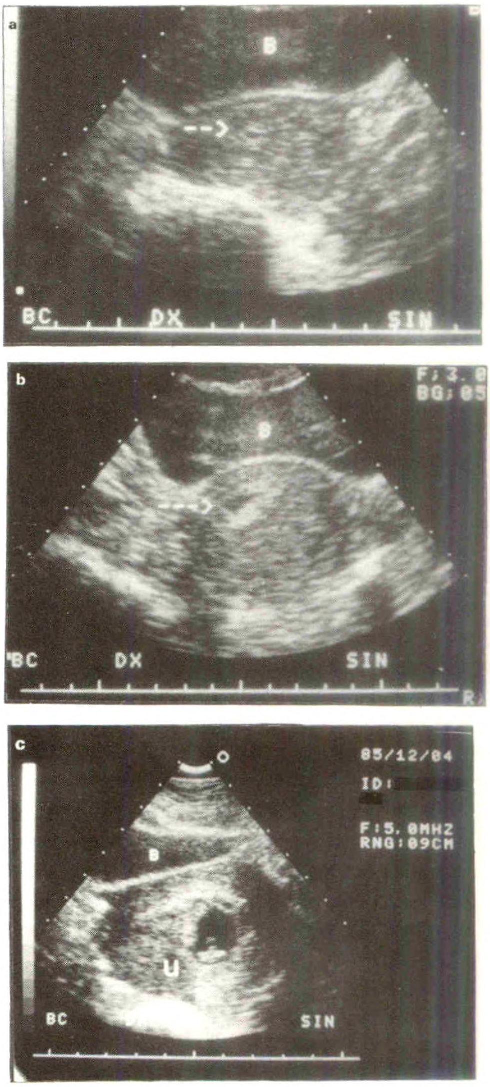

Fig. 2. Sonograph showing an eccentric ring of 4 mm (arrowhead) in association with a serum hCG level of 894 i.u./l (a). Repeated scans confirmed a normal intrauterine pregnancy (b and c). B, Bladder; U, uterus; DX, right side; SIN, left side; BC, operator.

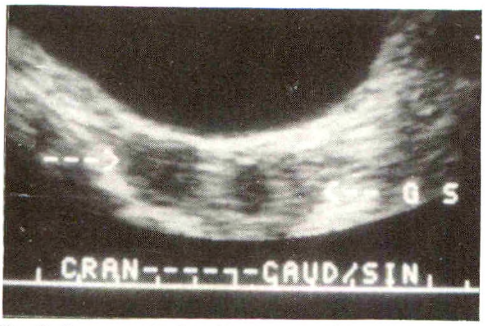

Fig. 3. Sonograph showing an ectopic gestational sac as an adnexal ring with a thick echogenic contour (GS). The left ovary is seen close to the sac (arrowhead).

surgically. In seven the ultrasound picture remained unchanged and serial hCG assays showed constant or decreasing levels. Curettage was performed and a miscarriage was diagnosed. One patient did not come for review as required but returned as an emergency case with ruptured ectopic pregnancy 1 week later.

In the total series the ultrasound scan on admission identified ectopic pregnancy in 71% of the women (29/41). Eight more were correctly diagnosed by repeated sonography, thus 90% of the ectopic pregnancies were detected by this method.

There were no false positive hCG results and trophoblastic tissue was detected in all the women. In 24% of the ectopic pregnancies the hCG level was below 100 i.u./l and in 25% above 6500 i.u./l. The lowest hCG level in this group was 48 i.u./l and the highest 13 500 i.u./l. In all cases in which an empty uterus was observed by sonography (groups C, D and E) and the hCG level was above 1000 i.u./l, an ectopic pregnancy was found.

Discussion

The diagnosis of ectopic pregnancy has been greatly improved by the introduction of rapid and sensitive assay for hCG (Seppälä *et al.* 1981; Stenman *et al.* 1982), but ectopic and intrauterine pregnancies cannot be differentiated on the basis of the hCG level. By sonography it is often possible to locate the pregnancy properly if reference to the hCG level is made (Kadar *et al.* 1981; Romero *et al.* 1985). Nevertheless, the reliability of this technique can be affected by poor display due to obesity or uterine position, operator experience and equipment resolution. On the basis of a large retrospective study Tuomivaara *et al.* (1986) questioned the value of sonography.

In the present study we used ultrasound findings to guide the management of suspected ectopic pregnancy by categorizing the results into five groups. No false negative and only one false positive result occurred. With this approach there was only one unnecessary laparoscopy where adhesions had suggested the presence of cul-de-sac fluid.

Fetal echoes were identified by sonography in only four ectopic pregnancies. Most of the ectopic pregnancies were suspected because of the presence of cystic adnexal masses characterized by a thick echogenic contour (Fig. 3). This sign was related to the presence of an unruptured ectopic sac and the thick echogenic contour observed by sonography is likely to be due to chorionic tissue. We found this ultrasonic sign reliable in identifying an ectopic gestational sac as also suggested by Coleman *et al.* (1985*b*). In the other ectopic pregnancies complex adnexal masses were detected (Fig. 4) apparently due to bleeding and in women with more massive findings, due to rupture. This finding is not specific, a similar picture is seen with tubo-ovarian abscesses, rupture of corpus luteum cysts and endometriosis (Laing & Jeffrey 1983). Nevertheless, the presence of an adnexal mass with an empty uterine cavity in combination with a positive pregnancy test is strongly suggestive of ectopic pregnancy and therefore requires surgical confirmation.

In our study the hCG level was below 100 i.u./l in 24% of the proven ectopic pregnancies.

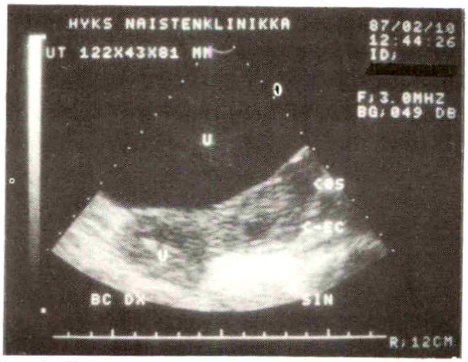

Fig. 4. Ectopic pregnancy suspected by ultrasound because of the presence of complex adnexal mass (EC) and an empty uterus (lower U). The left ovary is identified (OS).

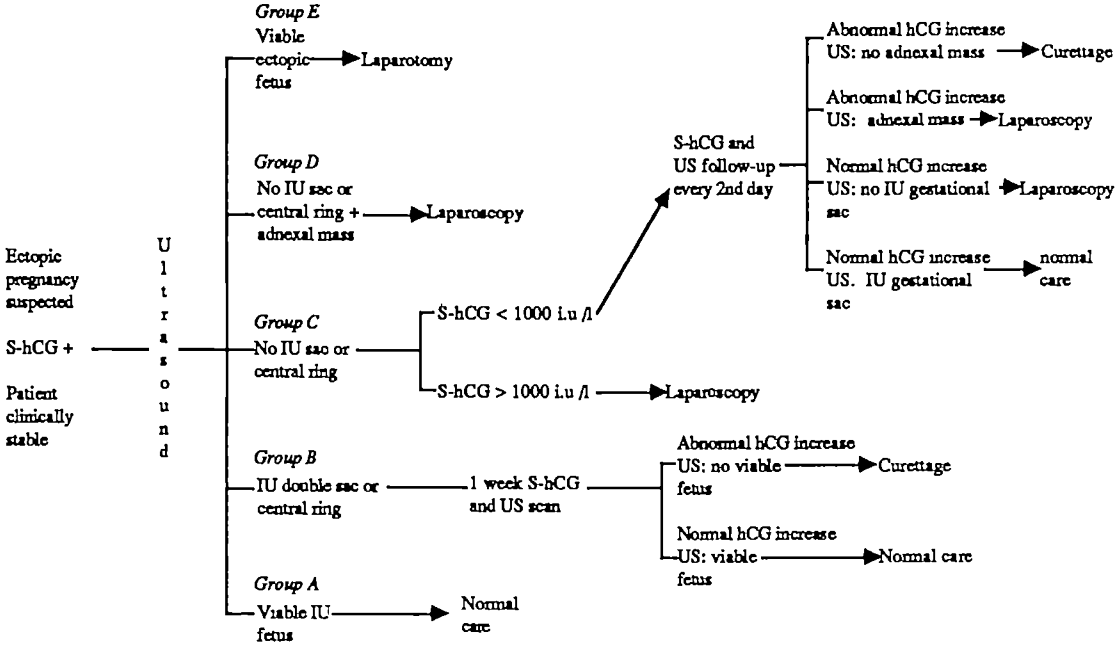

Fig. 5. Algorithm for follow-up and treatment of patients suspected of havng an ectopic pregnancy. Decision on treatment is based on sonographic findings and assay of serum human chorionic gonadotrophin (S-hCG). IU, Intrauterine; US, ultrasound

Romero *et al.* (1985*b*) also found very low hCG concentrations in 11·9% of the ectopic pregnancies in their series. The use of a hCG assay with a low threshold is therefore important. We used an immunofluorometric assay with a sensitivity of 0·2 i.u./l and a cut-off value of 10 i.u./l which did not give any false negative results.

Using the double sac sign and identifying eccentrically located intrauterine rings as an early gestational sac we detected intrauterine pregnancy with a predictive value of 100%. In fact a gestational sac can be recognized by the presence of decidua capsularis and parietalis in close apposition which appear at ultrasound as a sac surrounded by a double concentric ring (Bradley *et al.* 1982; Nyberg *et al* 1983). However, when the sac is very small, mean diameter <10 mm, it is difficult to identify clearly the two decidua. In these cases we recognized a real intrauterine sac as an eccentrically located transsonic ring as also indicated by Abramovici *et al* (1983). Using these ultrasound criteria, we were able to identify a normal intrauterine pregnancy or miscarriage at hCG levels below 6500 mi.u./ml, the discriminatory zone suggested by Kadar *et al* (1981) (Fig. 2). This corresponds to 3600 i.u./l in our assay (2nd IS). With high resolution ultrasound equipment an intrauterine gestational sac with a diameter of 4–5 mm has been identified at a hCG level of 1800 mi.u./ml (2nd IS) (Nyberg *et al.* 1986). In this study the smallest gestational sac observed was 4 mm and the corresponding hCG level 894 i.u./l, in association with a normal pregnancy.

It would be valuable if a lower hCG level could be used as 'discriminative zone' because the hCG levels in ectopic pregnancies are rarely above 6500 mi.u./ml (Cartwright & Di Pietro 1984; Romero *et al.* 1985). In the present study we always detected an ectopic pregnancy in the absence of a gestational sac and an hCG level >1000 i.u./l.

In the presence of an hCG level below the 'discriminative zone' together with a sonographic picture indicative of neither an intrauterine nor ectopic pregnancy, serial hCG assay and ultrasound surveillance is useful (Romero *et al.* 1985). We used a similar approach for the patients categorized as group C, and a correct diagnosis was reached during follow-up in all of them. Except for one woman, who did not attend for follow-up, no tubal rupture occurred. By adopting a discriminative hCG level of 1000 i.u./l (2nd IS) and ultrasound assessment, the number of patients needing further observation would be reduced.

In conclusion the ultrasound criteria used in this study allowed early identification and correct management in all patients suspected of having ectopic pregnancy. This approach limits the number of complications and unnecessary surgery. On the basis of these data we suggest using the algorithm in Fig. 5.

Acknowledgments

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References

Abramovici, H , Auslender, R., Lewin, A. & Faktor, J. K. (1983) Gestational-pseudogestational sac: a new ultrasonic criterion for differential diagnosis *Am J Obstet Gynecol* **145,** 377-379.

Batzer, F. R. & Corson, S. L. (1986) Diagnostic techniques used for ectopic pregnancy *J Reprod Med* **31,** 86-93.

Bradley, W. G., Fiske, C E. & Filly, R. A (1982) The double sac sign of early intrauterine pregnancy: use in exclusion of ectopic pregnancy. *Radiology* **143,** 223-226

Campbell, S., Goswamy, R., Goessens, L. & Whitehead, M. (1983) Real-time ultrasonography for determination of ovarian morphology and volume. *Lancet* **i,** 425-427.

Cartwright, P. S. & Di Pietro, D. L. (1984) Ectopic pregnancy: changes in serum human gonadotropin concentration. *Obstet Gynecol* **63,** 76-80.

Coleman, B. G., Baron, R. L , Arger, P. H., Arenson, R L , Axel, L., Mayer, D. P. & Costello, P. (1985) Ectopic embryo detection using real time sonography. *J Clin Ultrasound* **13,** 545-554.

Kadar, N., DeVore, G. & Romero, R (1981) Discriminatory hCG zone: its use in the sonographic evaluation for ectopic pregnancy. *Obstet Gynecol* **58,** 156-161.

Laing, F C. & Jeffrey, B. R. (1983) Ultrasound evaluation of ectopic pregnancy In *Ultrasonography in Obstetrics and Gynecology* (Callen, P. W., ed.), W B. Saunders Company, Philadelphia, pp. 291-304.

Marks, W. M., Filly, R. A , Callen, P W & Laing, F C. (1979) The decidual cast of ectopic pregnancy a confusing ultrasonographic appearance *Radiology* **133,** 451-454

Nyberg, D A , Laing, F. C., Filly, R. A., Uri-Simmons, M & Brooke, J. Jr (1983) Ultrasonographic differentiation of the gestational sac of early intrauterine pregnancy from the pseudogestational sac of ectopic pregnancy. *Radiology* **146,** 755-759

Nyberg, D A., Filly, R. A., Duarte Filho, D. L , Laing, F. C & Mahoney, B. S. (1986) Abnormal pregnancy: early diagnosis by US and serum chorionic gonadotropin levels *Radiology* **158,** 393-396.

Romero, R , Kadar, N., Jeanty, P., Copel, J A , Chervenak, F. A., DeCherney, A & Hobbins, J. C. (1985*a*) Diagnosis of ectopic pregnancy: value of the discriminatory human chorionic gonadotropin zone. *Obstet Gynecol* **66,** 357-360.

Romero, R , Kadar, N., Copel, J. A , Jeanty, P., DeCherney, A. H. & Hobbins, J. C (1985*b*) The effect of different human chorionic gonadotropin assay sensitivity on screening for ectopic pregnancy. *Am J Obstet Gynecol* **153,** 72-74

Romero, R., Kadar, N , Copel, J. A., Jeanty, P., DeCherney, A H & Hobbins, J. C. (1986) The value of serial human chorionic gonadotropin testing as a diagnostic tool in ectopic pregnancy *Am J Obstet Gynecol* **155,** 392-394

Seppälä, M , Ranta, T., Rutanen, E. M., Stenman, U-H., Tontti, K. & Chard, T (1981) Improved diagnosis of pregnancy-related gynaecological emergencies by a rapid human chorionic gonadotrophin beta-subunit assay. *Br J Obstet Gynaecol* **88,** 138-140

Stenman, U-H , Tanner, P., Ranta, T , Schroder, J. & Seppala, M. (1982) Monoclonal antibodies to chorionic gonadotropin. use in a rapid radioimmunoassay for gynecologic emergencies. *Obstet Gynecol* **59,** 375-378

Stenman, U-H., Alfthan, H., Myllynen, L. & Seppälä, M. (1983) Ultrarapid and highly sensitive time-resolved fluoroimmunometric assay for chorionic gonadotropin. *Lancet* **ii,** 647-649.

Tuomivaara, L , Kauppila, A. & Puolakka, J. (1986) Ectopic pregnancy: an analysis of the etiology, diagnosis and treatment in 552 cases *Arch Gynecol* **237,**135-147.

Weckstein, L. N. (1985) Current perspective on ectopic pregnancy. *Obstet Gynecol Surv* **40,** 259-272.

Weckstein, L N., Boucher, A. R., Tucker, H., Gibson, D. & Rettenmair, M A. (1985) Accurate diagnosis of early ectopic pregnancy. *Obstet Gynecol* **65,** 393-397

Wexler, S., Yedwab, G., Golan, A. & David, M. P (1984) Pseudogestational sac in ectopic pregnancy. *Acta Obstet Gynecol Scand* **63,** 63-65.

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Is postoperative radiotherapy or maintenance chemotherapy necessary for carcinoma of the uterine cervix?

KENJI SHIROMIZU, MASUMI MATSUZAWA,
MICHIKO TAKAHASHI, OSAMU ISHIHARA

Summary. The effectiveness of postoperative radiotherapy and adjuvant chemotherapy was examined for patients with uterine cervical squamous cell carcinoma. Whole pelvis irradiation is unnecessary for patients with less than 2/3 of depth of cervical local involvement without pelvic regional lymph node metastases. Adjuvant chemotherapy with tegafur [1-(2-tetrahydrofuryl)-5-fluorouracil] (600 mg/day) has failed to improve the survival of patients with positive lymph node metastases.

Although excellent results are achieved in patients with carcinoma *in situ* or with early stromal invasion (stages 0 or Ia) of the uterine cervix, most patients with advanced stage cervical carcinoma or pelvic lymph node metastases have a very poor prognosis. In an attempt to improve their survival, various regimens of postoperative radiotherapy and/or adjuvant anti-cancer chemotherapy are given. Radiotherapy and chemotherapy are associated with serious short- and long-term complications, so that the choice of treatment should be based on an assessment of risk-benefit. In this review paper we have tried to identify factors which would permit selection of patients who would receive benefit from radiotherapy or chemotherapy for cervical squamous cell carcinoma.

Patients and methods

From 1 November 1975 to 31 December 1983, 684 patients with uterine cevical carcinoma were treated at Saitama Cancer Center Hospital. Of the 328 patients who had surgery, 273 with obvious cervical invasion (excluding stages 0 and Ia) underwent abdominal radical hysterectomy, and histopathological examination of both local cervical involvement and pelvic lymph node metastases. Of the 273 patients 63 had pelvic lymph node metastases. Based on the depth of cervical invasion, the following classifications were adopted; α-type, invasion within ⅓ depth; β-type, from ⅓ to ⅔; γ-type, from ⅔ to total depth; pm-type, positive invasion of the parametrium External whole pelvis radiotherapy by Linac (50 Gy) was given to all patients with lymph node metastasis, to all those with γ-type and pm-type invasion, and to some patients with α-type and β-type invasion without positive lymph nodes. Intravaginal irradiation (up to three times) was also given to some patients with vaginal involvement. Oral administration of tegafur [1-(2-tetrahydrofuryl)-5-fluorouracil] (600 mg/day) was given to 34 patients with positive lymph node metastases. Follow-up data were available till death or 31 December 1985.

The patients were classified according to WHO histological findings (Poulsen & Taylor 1973) and clinical staging was based on the FIGO (1971) staging classification. The patients considered acceptable for this study had squamous cell carcinoma (54 patients with and 184

Division of Gynaecology, Saitama Cancer Center, Saitama, Japan
KENJI SHIROMIZU
MASUMI MATSUZAWA
MICHIKO TAKAHASHI
OSAMU ISHIHARA

Correspondence. Kenji Shiromizu, MD, Tochigi Cancer Center, Yonan 4-9-13 Utsunomiya, Tochigi 320, Japan

Table 1. Clinical data of patients with α- and β-type invasion without lymph node metastasis

	α-type		β-type	
	No radiotherapy	Radiotherapy	No radiotherapy	Radiotherapy
Number of patients	46	12	20	18
Age (years) mean	49·2	51·8	52·4	46·2
(SD)	(10·0)	(10·5)	(9·1)	(12·3)
Histological diagnosis				
Keratinizing	9	1	1	2
Non-keratinizing				
Large-cell	34	8	15	14
Small-cell	3	3	4	2
Clinical stage				
Ib	37	2	14	8
IIa	2	6	0	3
IIb	7	4	6	7

patients without lymph node metastases), excluding adenocarcinoma (19), adenosquamous cell carcinoma (12), undifferentiated carcinoma (2) and two patients with squamous cell carcinoma whose death was caused by therapeutic procedures.

Results

Negative lymph node metastasis

Clinical data of all patients with α- and β-type invasion without lymph node metastasis are shown in Table 1. There were no recurrences in the 58 α-type patients, of whom 12 had further postoperative radiotherapy (external in three and vaginal in nine) (Table 2). One of 20 β-type patients without radiotherapy had a vaginal cuff recurrence 3 months after radical hysterectomy. That recurrent carcinoma, a large-cell non-keratinizing carcinoma, was completely eradicated by 60 Gy external irradiation and she was well 7 years after the second treatment (Table 2). There were no recurrences in the 18 β-type patients who received further postoperative radiotherapy (external in 14, external and vaginal in three, and vaginal only in one) (Table 2).

Table 2. Recurrent sites and lymph node metastasis

	No of positive nodes		
	0	1–2	≥3
α-type	*0/46 0/12	0/1	0/0
β-type	*1/20 0/18 $\begin{pmatrix}1\\0\\0\end{pmatrix}$	1/7 $\begin{pmatrix}0\\0\\1\end{pmatrix}$	1/1 $\begin{pmatrix}0\\0\\1\end{pmatrix}$
γ-type	15/53 $\begin{pmatrix}4\\2\\9\end{pmatrix}$	4/12 $\begin{pmatrix}3\\0\\1\end{pmatrix}$	4/4 $\begin{pmatrix}0\\3\\1\end{pmatrix}$
pm-type	12/35 $\begin{pmatrix}5\\0\\7\end{pmatrix}$	6/18 $\begin{pmatrix}0\\2\\4\end{pmatrix}$	8/11 $\begin{pmatrix}0\\4\\4\end{pmatrix}$

Figures in parenthesis are for recurrent sites. Top—intrapelvic; middle—intra- and extrapelvic; bottom—extrapelvic. *Without radiotherapy.

The recurrence rates in γ- and pm-type patients were 28·3% and 34·3%, respectively. Of these the recurrence was extrapelvic in 73·3% of the patients with γ-type and in 58·3% of those with pm-type invasion (Table 2).

Positive lymph node metastasis

Only one of the eight patients with α- and β-type invasion and not more than two positive lymph nodes had a recurrence (Table 2). One third of both the γ- and pm-type patients with not more than two positive nodes had a recurrence, but 70% of their recurrences were extrapelvic. The patients with three or more positive nodes had much higher rates of recurrences (72·7–100%). All recurrent sites included extrapelvic regions (Table 2).

Postoperative anti-cancer chemotherapy (tegafur 600 mg/day) was given to 34 patients whereas the other 20 were not given chemotherapy. Figure 1 shows the survival of both groups by the Kaplan–Meier method. There was no significant difference in survival between

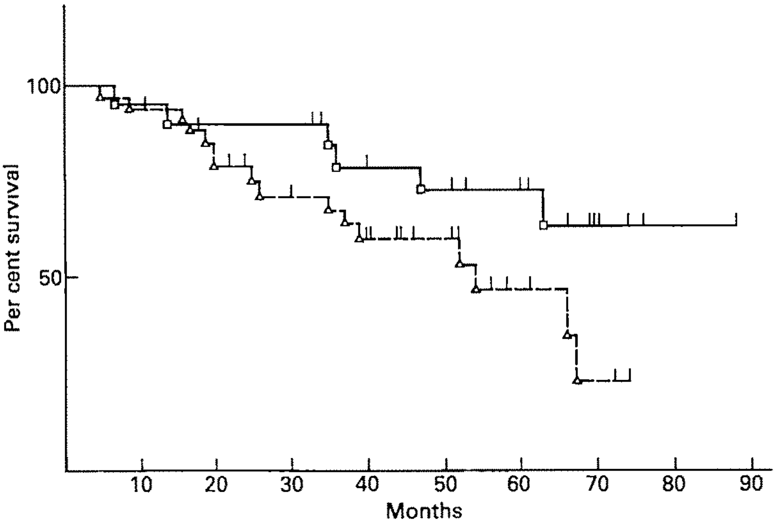

Fig. 1. Survival of patients with positive nodes with (---) and without (—) chemotherapy.

chemotherapeutic and non-chemotherapeutic groups (Cox–Mantel analysis $P=0{\cdot}103$).

Discussion

Although pre-operative radiotherapy may eradicate lymph node metastases in some patients with cervical carcinoma, it is questionable whether postoperative radiotherapy prevents local recurrence and improves survival (Lagasse *et al.* 1974; Larson *et al.* 1987). Since radiotherapy also carries some morbidity, indications for its use should be based on the relative risk and benefit for the patients (Larson *et al.* 1987).

The greater the depth of cervical invasion and the greater the number of lymph node metastases, the higher the recurrence rates (Piver & Chung 1975). So histological assessment of the degree of local carcinoma spread is useful for predicting high risk of recurrence. In this study, no patient with α-type invasion (involvement within inner ⅓ of cervical wall) without node metastasis had a recurrence, irrespective of whether or not postoperative radiotherapy was given. Of the 20 patients with β-type invasion and negative lymph nodes, only one had a vaginal cuff local recurrence. In patients with γ- and pm-type invasion the recurrence rates did not differ between those without lymph node metastases and those with one or two positive lymph nodes. Because in this study γ- and pm-type patients with or without lymph node involvement, and all α- or β-type patients with lymph node metastases received postoperative external irradiation, it is not clear whether postoperative radiotherapy is necessary for reducing local recurrence.

However, adjuvant postoperative radiotherapy may benefit patients with pelvic lymph node metastases treated with radical hysterectomy and pelvic lymphadenectomy (Creasman *et al.* 1986; Hogan *et al.* 1982; Larson *et al.* 1987). It is therefore our current opinion that postoperative external radiotherapy could be withheld in β-type patients without nodal disease with a 5% risk of local recurrence, but that radiotherapy is necessary for all patients with γ- and pm-type invasion and all those with α- and β-type invasion with positive nodes.

Although postoperative radiotherapy may reduce the prevalence of pelvic recurrences and improve survival (Creasman *et al.* 1986; Hogan *et al.* 1982; Larson *et al.* 1987), most recurrence sites in patients with lymph node metastasis are extrapelvic (Fuller *et al.* 1982). So to prevent distant metastasis and improve survival, systemic administration of anti-cancer drugs is thought to be useful (Ueki *et al.* 1983). Although we failed to achieve good results in this respect by oral administration of tegafur to patients with positive lymph nodes, the search for a drug or combination of drugs which can salvage the lives of those whose cervical carcinoma has spread to the pelvic lymph nodes must continue.

References

Creasman, W. T., Soper, J. T. & Clarke-Peason, D. (1986) Radical hysterectomy as therapy for early carcinoma of the cervix. *Am J Obstet Gynecol* **115**, 964-969.

FIGO (1971) Classification and staging of malignant tumours in the female pelvis. New York, 12 April 1970. *Acta Obstet Gynecol Scand* **50**, 1-7.

Fuller, A F., Elliott, N , Kosloff, C. & Lewis, J L. Jr (1982) Lymph node metastases from carcinoma of the cervix, Stage IB and IIA: implications for prognosis and treatment. *Gynecol Oncol* **13**, 165-174

Hogan, W. M., Littman, P., Gringer, L , Miller, C. L & Mikuta, J. J. (1982) Results of radiation therapy given after radical hysterectomy. *Cancer* **49**, 1278-1285.

Lagasse, L. D., Smith, M L , Moore, J. G., Morton, D. G., Jacobs, M., Johnson, G. H. & Watring, W. G. (1974) The effect of radiation therapy on pelvic lymph node involvement in Stage I carcinoma of the cervix *Am J Obstet Gynecol* **119**, 328-334.

Larson, D. M , Stringer, C A , Copeland, L J , Gershenson, D. M , Malone, J. M Jr & Rutledge, F. N. (1987) Stage IB cervical carcinoma treated with radical hysterectomy and pelvic lymphadenectomy: role of adjuvant radiotherapy *Obstet Gynecol* **69**, 378-381.

Piver, M. S. & Chung, W. S (1975) Prognostic significance of cervical lesion size and pelvic node metastases in cervical carcinoma. *Obstet Gynecol* **46**, 507-510.

Poulsen, H. E & Taylor, C W (1973) Histological typing of female genital tract tumours. *International Histological Classification of Tumours, No 13.* WHO, Geneva, pp. 55-59.

Ueki, M., Maeda, T., Okamura, S , Kanda, T., Sano, T. & Sugimoto, O. (1983) Study on the effect of classification and adjuvant surgical chemotherapy for cervical carcinoma. (In Japanese.) *J Jpn Soc Cancer Ther* **18**, 927-939

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Thyroxine concentration and outcome of hyperemetic pregnancies

R. K. H. CHIN, T. T. H. LAO

Summary. Plasma total thyroxine (TT4) and free thyroxine (FT4) were measured in 23 women with hyperemesis gravidarum at presentation, on average at about 10 weeks, in the second trimester, and before delivery. The first TT4 was raised abnormally in eight women and the FT4 in nine, but by the second trimester the TT4 was abnormally high in only three although in eight the FT4 remained high. By the third trimester all measurements, except one slightly raised FT4, were normal. Birthweight was not related to the thyroxine levels but there was a weak significant negative correlation between FT4 in the second trimester and gestational age at delivery.

The association between abnormal thyroid function and hyperemesis gravidarum has been well documented (Bouillon *et al.* 1982). Although thyroid function was found to be unrelated to the severity of morning sickness (Evans *et al.* 1986), in some patients the degree of hyperthyroidism has been severe enough to warrant antithyroid drug treatment (Jeffcoate & Bain 1985; Lao *et al.* 1986). However, the outcome of pregnancy has not been correlated with the degree of hyperthyroidism. Since in thyrotoxic patients, the outcome of pregnancy is related to the protein-bound iodine and resin tri-iodothyronine uptake values (Mestman *et al.* 1974), we examined the relation between thyroid hormones and the outcome of pregnancy in patients with hyperemesis gravidarum.

Patients and methods

Twenty-three patients admitted to our hospital because of hyperemesis gravidarum were included in the study. The mean gestation on admission was 9·9 weeks (range 6–20 weeks).

A sample of blood was taken from each patient on admission. Plasma total thyroxine (TT4) was estimated by the Syva EMIT method adapted for use on the Cobas-Bio centrifugal analyser, and free thyroxine (FT4) was estimated by radioimmunoassay using commercial kits (Diagnostic Products Corporation). Repeat blood samples were taken from these patients every 2 weeks until the thyroid hormones returned to normal levels. Further samples were taken at the end of the second trimester and between 35 weeks and delivery.

All the patients were followed up until delivery. The gestational age and birthweight at delivery were correlated with the TT4 and FT4 values at presentation (TT4 1 and FT4 1), at the end of the second trimester (TT4 2 and FT4 2), and before delivery (TT4 3 and FT4 3).

Results

At presentation, eight of the 23 hyperemetic patients had a TT4 value above our normal laboratory reference range for first trimester of pregnancy (>180·5 nmol/l), and nine of them also had a raised FT4 value (>30·1 pmol/l). By the second trimester, three patients had a TT4 above the reference range for the second trimester of pregnancy (>178·9 nmol/l) but eight patients still had a raised FT4 (>23·6 pmol/l). By the third trimester, all the patients had a normal TT4 (<188·6 nmol/l) and only one patient had a FT4 just above the normal laboratory range for

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Department of Obstetrics and Gynaecology, Prince of Wales Hospital, Shatin, Hong Kong
R K H. CHIN *Senior Medical Officer*
T. T H. LAO *Lecturer*

Correspondence: Dr R. K H Chin

the third trimester (>24·7 pmol/l). The highest FT4 was present in a patient who presented at 13 weeks gestation. Her initial FT4 was 100·3 pmol/l. Her thyroid function remained abnormal at 25 weeks and she received an 8-week course of carbimazole with good response. Her thyroid function then remained normal until 4 months after delivery when she developed postpartum thyrotoxicosis, and she was treated with carbimazole and propranolol. In retrospect, this patient probably developed Graves' disease for the first time during pregnancy, and the remission induced with carbimazole lasted only about 4 months after delivery. All the other patients with hyperthyroxinaemia recovered spontaneously after an interval of between 2 and 11 weeks.

Two patients had spontaneous preterm labours and were delivered at 36 weeks. Another four patients were delivered at between 37 and 38 weeks after spontaneous labours. The rest were delivered between 38 and 42 weeks gestation. There was no correlation between the birthweight or gestation at delivery and total or free thyroxine levels at any stage except for FT4 2 which showed a weak but significant negative correlation ($P<0{\cdot}04$) with gestational age at delivery (Table 1).

Discussion

In pregnant women with untreated hyperthyroidism, the fetus is at risk of preterm labour and intrauterine growth retardation (Sugrue & Drury 1980) The outcome of the pregnancy in these patients appeared to be related to the thyroid hormone levels at presentation and after treatment (Mestman *et al.* 1974). In patients with hyperemesis gravidarum, transient hyperthyroidism is common, and it has been shown that these women give birth to babies that are lighter than those born to hyperemetic women with normal thyroid function (Bouillon *et al.* 1982). On the other hand, Lao *et al.* (1987) reported that the outcome of pregnancies in patients with transient hyperthyroidism associated with hyperemesis gravidarum was not significantly different from that in patients without hyperthyroxinaemia. However, in that study we did not examine the relation between the actual thyroid hormone levels and the fetal outcome; it is possible that the lower birthweight reported for hyperthyroxinaemic hyperemetic women may in fact be related to a smaller gestational age at delivery in some of these women.

In the present longitudinal study we followed up the changes in total and free thyroxine levels in these patients. It was found that the outcome of pregnancy was unrelated to the severity of hyperthyroxinaemia at presentation, although there was a significant negative correlation between free thyroxine concentration at the second trimester and gestation at delivery, but not with birthweight. This finding suggests that although transient hyperthyroidism does not lead to intrauterine growth retardation, hyperthyroxinaemia persisting into the second trimester may affect the duration of pregnancy. Although only two patients (8·7%) with hyperthyroxinaemia were delivered before 37 weeks, six patients (26·1%) had spontaneous labour before 38 weeks, suggesting that preterm labour may occur often enough to warrant special attention to be paid to these patients. It is useful to monitor total and free thyroxine levels into the second trimester. If the free thyroxine level is still high, there is a considerable risk of preterm labour and these patients need to be monitored closely and to have delivery arranged in a hospital.

Although antithyroid treatment is highly effective for symptomatic control (Jeffcoate & Bain 1985; Lao *et al.* 1986), there is still no evidence to show that this treatment will alter the outcome of pregnancy (Bouillon *et al.* 1982). Our experience showed that most patients with transient hyperthyroidism of pregnancy had spontaneous resolution of their hyperthyroidism, and treatment should be withheld unless the abnormality persists into the second trimester. However, patients requiring antithyroid treatment should be reassessed up to 1 year post-

Table 1. Correlation (*r*) between total (TT4) and free thyroxine (FT4) concentration and outcome of pregnancy

	TT4 1	TT4 2	TT4 3	FT4 1	FT4 2	FT4 3
Birthweight	−0·048	−0·266	−0 176	−0·274	−0·268	−0·022
Gestation at delivery	−0·051	−0·259	0·006	−0·252	−0·434*	0·005

* $P = 0{\cdot}0384$ (*t*-test).

partum to exclude cases of Graves' disease presenting as hyperemesis gravidarum.

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References

Bouillon, R., Naesens, M., van Assche, F. A *et al.* (1982) Thyroid function in patients with hyperemesis gravidarum *Am J Obstet Gynecol* **143,** 922-926.

Evans, A J., Li, T. C., Selby, C & Jeffcoate, W. J (1986) Morning sickness and thyroid function. *Br J Obstet Gynaecol* **93,** 520-522.

Jeffcoate, W J & Bain, C. (1985) Recurrent pregnancy-induced thyrotoxicosis presenting as hyperemesis gravidarum. *Br J Obstet Gynaecol* **92,** 413-415.

Lao, T T. H., Chin, R K. H., Cockram, C S. & Panesar, N. S. (1986) Transient hyperthyroidism in hyperemesis gravidarum. *J R Soc Med* **79,** 613-615

Lao, T. T , Chin, R. K. H. & Chang, A. M. Z. (1987) The outcome of hyperemetic pregnancies complicated by transient hyperthyroidism *Aust NZ J Obstet Gynecol* **27,** 99-101.

Mestman, J. H., Manning, P. R & Hodgman, J (1974) Hyperthyroidism and pregnancy. *Arch Intern Med* **134,** 434-439

Sugrue, D. & Drury, M I. (1980) Hyperthyroidism complicating pregnancy Results of treatment by antithyroid drugs in 77 pregnancies. *Br J Obstet Gynaecol* **87,** 970-975.

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Patterns of growth of uterine leiomyomas during pregnancy. A prospective longitudinal study

ARIEL AHARONI, ALEXANDER REITER, DAVID GOLAN,
YOAV PALTIELY, MORDECHAI SHARF

Summary. In a prospective study 32 leiomyomas (fibroids) in 29 pregnant women were examined with ultrasound every 3–8 weeks. Each patient had between 3 and 6 scans (mean 4·4) during the course of pregnancy, and 13 patients had a final scan at 6 weeks postpartum. An individual growth curve was established for each tumour and the patterns of growth were analysed. No increase in size during the pregnancy was observed in 25 fibroids (78%). Only 7 (22%) increased in size but by no more than 25% of the initial volume. At 6 weeks postpartum the size of the fibroids did not differ significantly from the size during pregnancy.

Leiomyomas or fibroids are the most common uterine tumours and they are often associated with pregnancy (Jones & Jones 1982). There is a common belief that uterine fibroids grow during pregnancy (Pritchard *et al.* 1985; Moore & Morton 1986), but prospective data to support this belief are lacking. To check this assumption we have examined the growth pattern of leiomyomas during pregnancy in a prospective longitudinal study. We also studied the relation between the growth pattern and complications of pregnancy.

Patients and methods

The study population consisted of 29 pregnant women between 25 and 39 years of age (mean 33) who either were known to have uterine fibroids before pregnancy or were found to have them on routine ultrasound examination. Three of these patients had two distinct myomas each, so in all, 32 fibroids were followed in the study. We only included patients who had their initial scan during the first half of pregnancy (between 7 and 20 weeks gestation, mean 14·9 weeks). They were examined with ultrasound every 3–8 weeks throughout the pregnancy. Each patient had between 3 and 6 measurements (mean 4·4), and about half of them had a final one at 6 weeks postpartum.

All the scans were performed by the same examiner, with the use of an Aloka SSD-256 real time linear scanner. Each fibroid was photographed in two different perpendicular planes, and the volume of the tumour was calculated according to the formula for the volume of an ellipsoid as illustrated in Fig. 1.

The volume of each fibroid was plotted against the gestational age and a growth curve was established. All the women were asked to report any symptoms such as uterine contractions, abnormal bleeding and abdominal pain; these were recorded and related to the pattern of growth. Every woman was scheduled to have an ultrasound scan 6 weeks after delivery and this was compared with the last measurement before delivery. Analysis of the data included a percentage calculation of the volume change for each fibroid.

The accuracy of the measurements was confirmed in two ways. First, before starting the

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Department of Obstetrics and Gynecology, Haifa Medical Center (Rothschild), Haifa, Israel
ARIEL AHARONI
ALEXANDER REITER
DAVID GOLAN
YOAV PALTIELY
MORDECHAI SHARF

Correspondence: A Aharoni

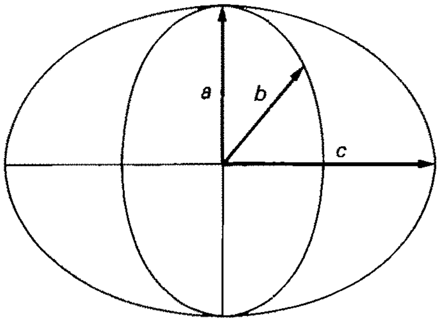

Fig. 1. Calculation for the volume (V) of an ellipsoid

$$V = \frac{4\pi abc}{3}$$

where $\pi = 3{\cdot}14$ and abc are the radii

study we made ultrasound measurements of fibroids in non-pregnant women scheduled for hysterectomy, and compared the linear measurements to the actual diameters of the fibroids after surgery. We found excellent correlation between these measurements. Second, in the six women who were delivered by caesarean section the fibroids were found to be the same size as was shown by the ultrasound measurements.

Results

Growth patterns

The growth curve of each single fibroid during the pregnancy is shown in Fig. 2. The change in size that occurred between the first and last measurement for each fibroid, starting with the smallest one (volume 7 cm^3) and ending with the largest one (volume 700 cm^3) is illustrated in Fig. 3.

Three different patterns of change could be identified. (i) Fibroids that grew by more than 10% of the initial volume. There were seven fibroids (22%) with this growth pattern but none of them increased by more than 25% from the initial volume. (ii) Fibroids that changed in size by less than 10% of the initial volume. There were 19 fibroids (59%) included in this group. (iii) Fibroids that decreased in size by more than 10%. Six fibroids (19%) showed a reduction in their size and the maximum reduction was 20%.

Postpartum assessment

Of the 29 women 13 were scanned 6 weeks after delivery and the fibroid was clearly detected in only five of them. Figure 4 compares the first and last measurements with the postpartum measurement of these five fibroids. The other eight fibroids could not be distinguished from the rest of the uterus which appeared uniformly enlarged.

Clinical assessment

Of the 29 women 20 (70%) complained at least once during pregnancy of mild generalized

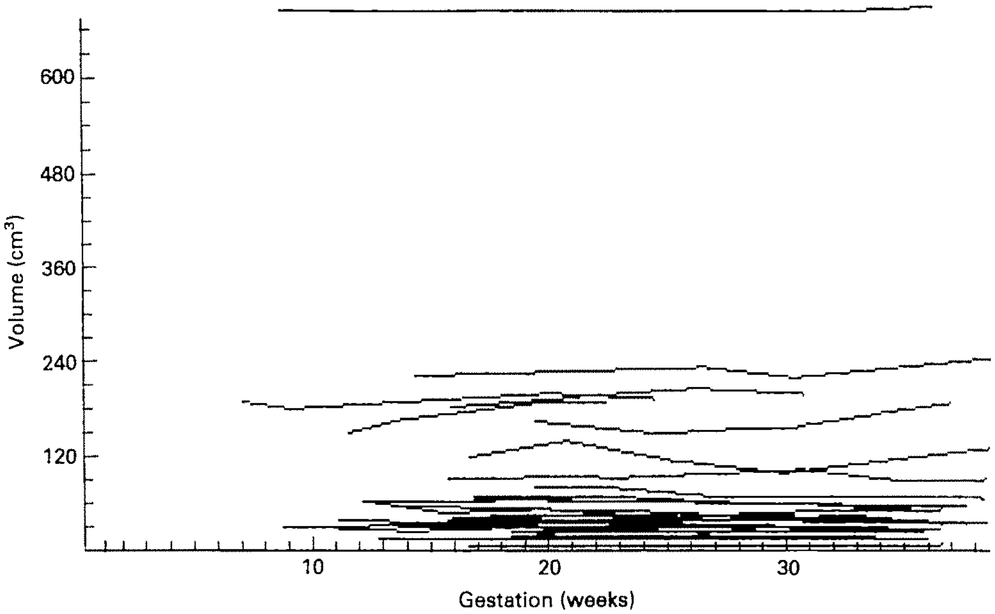

Fig. 2. Growth curves for 32 fibroids during pregnancy.

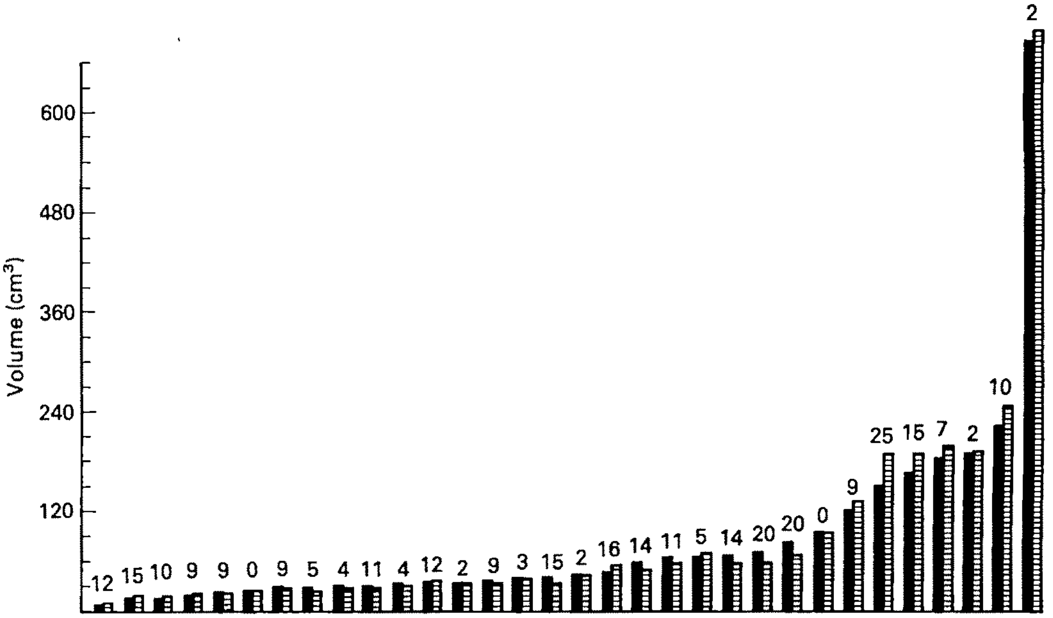

Fig. 3. Volume of 32 fibroids at first and last measurements (The numbers show the percentage change in volume.) ■, Initial volume; ⊟, final volume.

abdominal pain that did not require medication. Only three women required hospitalization for severe abdominal pain. They were successfully treated with bed-rest and analgesia.

Three women had preterm labours. One gave birth to twins at 35 weeks gestation and the other two had spontaneous deliveries at 36 weeks. There were no newborns below the 10th centile for birthweight. There were no obstetric complications such as placenta praevia or early separation of placenta. The caesarean section rate was 20%.

Discussion

There are a number of difficulties with the ultrasound diagnosis of fibroids during pregnancy. In the first trimester the fibroids may resemble tumours of the ovary, benign or malignant, and this is especially true for the corpus luteum of pregnancy. The cornua of a bicornuate uterus or localized areas of myometrial contractions may be mistaken for a fibroid (von Mickey 1977). In our series, the fibroids were followed serially and such mistakes were soon recognized.

In our prospective study we noted an increase in fibroid size during pregnancy in only 22%, but none of the fibroids increased by more than 25% of the initial volume. On the other hand, 19% of the fibroids decreased in size and the maximum reduction was less than 20%. Comparing the total volume of the fibroids calculated at the first ultrasound scan with the total volume calculated at the last scan showed a 3% increase in volume, which was not statistically significant.

Nearly 60% of the fibroids did not change in volume. A fibroid was considered unchanged if its volume on the last scan was within ±10% of the first measurement. We arrived at this value of 10% on empirical grounds by analysing the precision of our measurements and we believe that it is a good estimate for the theoretical precision. If 20% was the value chosen, nearly all the fibroids would be categorized as unchanged.

Measurements of fibroids during pregnancy have been available only in the last decade because of the improvement of ultrasound scanners. For this reason, data on fibroid growth in pregnancy are scarce, and we have not been able to find other prospective studies on the subject. However, in three recent retrospective studies the same pattern of fibroid growth has been observed. Muram *et al.* (1980) reported that 93% of the fibroids did not change during pregnancy, and in a larger series Winer-Muram *et al.* (1983) found no change in fibroid size in 92% of the women. Noia *et al.* (1983) reported a change in myoma size in only 11% of their series. These reports and our own findings are in contrast to the

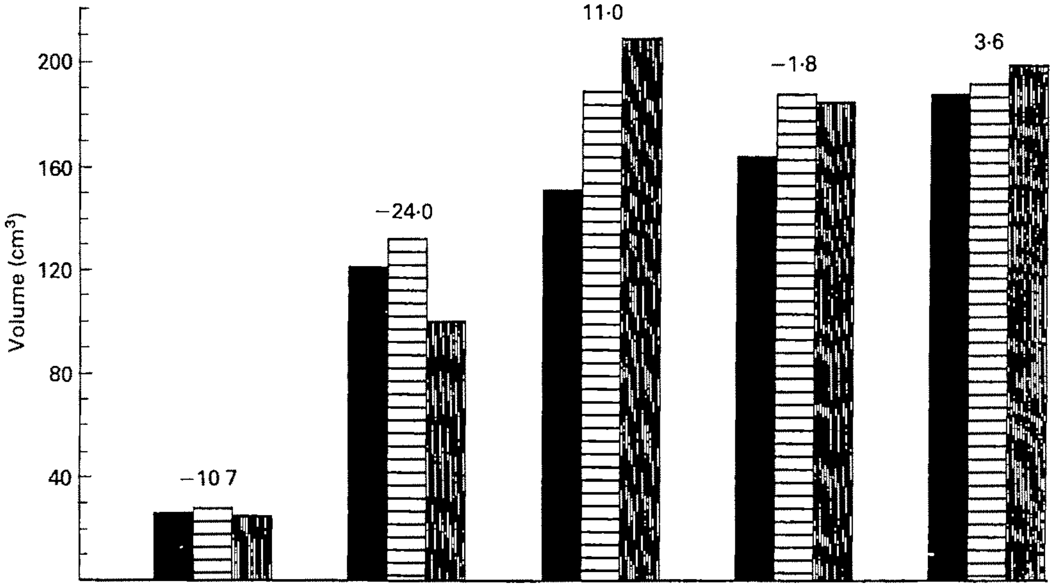

Fig. 4. Postpartum volume of fibroids compared with first and last volume (The numbers show the percentage change from the last volume) ■, Initial volume; ⊟, final volume, ▥, postpartum volume.

widespread opinion that fibroids grow during pregnancy.

In the series mentioned above, the fibroid volume was not calculated, and the magnitude of change was not stated. In our experience most fibroids changed shape during pregnancy, mainly from a spherical shape to a more flattened or elongated ellipsoid, without changing their volume. We feel that a longitudinal study of fibroid diameter instead of volume cannot describe the change in fibroid size accurately.

It has been supposed that uterine fibroids become enlarged during pregnancy under the influence of oestrogens, and it has been suggested that such continuous growth is the cause of complications in pregnancy Our findings showed no growth of fibroids during the second and third trimesters. We could not investigate growth changes during the first trimester as only six women were scanned before 12 weeks gestation and none of them before 7 weeks. However, considering that at 6 weeks postpartum, we could not detect any decrease in fibroid size in the five women examined, it is likely that there was also no increase in fibroid size during the first trimester.

There were no major clinical complications during pregnancy or in labour except for a slightly higher caesarean section rate. We conclude therefore that a pregnant woman with uterine fibroids can expect no unusual growth of these tumours, and in most cases, an uncomplicated pregnancy and labour.

References

Jones, H W. & Jones, G S. (1982) *Novak's Textbook of Gynecology*. 10th edn, Williams & Wilkins, Baltimore, pp. 439-440.

Moore, J. G & Morton, D. J (1986) Leiomyomas of the uterus In *Gynecology and Obstetrics* (Sciarra, J J. & Droegemueller, W., eds), Vol. 1 , Harper & Row, Hagerstown, p 5

Muram, D., Gillieson, M. S. & Walters, J H, (1980) Myomas of the uterus in pregnancy Ultrasonographic follow-up *Am J Obstet Gynecol* **138**, 16-19

Noia, G , Masini, L , Mazzei, R , Conte, M. & Bellati, U (1983) Sorveglianza ecografica della miomatosi uterina in gravidanza *Minerva Ginecol* **35**, 1-7

Pritchard, J. A , MacDonald, P C. & Gant, N. F (1985) *Williams Obstetrics*. 17th edn, Appleton-Century-Crofts, Connecticut, pp 689-693

von Mickey, L. I (1977) Sonographic study of uterine fibromyomata in the non-pregnant state and during gestation. In *Ultrasonography in Obstetrics and Gynecology* (Saunders, R. D & James, A. E , eds), ACC, New York, pp. 297-331.

Winer-Muram, H. T , Muram, D., Gillieson, M S., Ivey, B J. & Muggah, H. F. (1983) Uterine myomas in pregnancy *Can Med Assoc J* **128**, 949-950

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Insulinoma and pregnancy. Case report

P. J. HALE, J. F. HALE, M. NATTRASS

Case report

A 41-year-old patient who had three children developed symptoms suggestive of hypoglycaemia with dizziness and double vision in the early morning soon after becoming pregnant for the fourth time. At 11 weeks gestation she had a missed abortion. Histology of the fetus revealed no obvious abnormality, and her hypoglycaemic symptoms subsided. Symptoms returned 4 months later with increasing frequency and the diagnosis of insulinoma was confirmed with the finding of an 18 h fasted blood glucose of 1·9 mmol/l with a simultaneous serum insulin concentration of 63 mU/l.

While plans were being made for surgical management she conceived again and this time her symptoms of hypoglycaemia remitted with the onset of pregnancy, though the first trimester was complicated by severe nausea and vomiting requiring in-patient care and the use of both oral and parenteral antiemetics. Throughout pregnancy she was advised to avoid alcohol and was electively fed at 03.00 hours. On this regimen pregnancy progressed normally with no episodes of symptomatic hypoglycaemia. Fasting blood glucose in hospital during the first trimester ranged from 1·9 to 6·4 mmol/l (mean 4·2 mmol/l; $n = 20$), and subsequent fasting home blood glucose measurements using BM 20-800 sticks (Boehringer Corporation (London) Ltd, Lewes, East Sussex) were reported to be around 4·4 mmol/l. At 36 weeks she went into spontaneous labour and was delivered of a normal 2·78 kg male infant (30th centile for gestational age) with Apgar scores of 8 at 1 min and 10 at 5 min.

At booking (12 weeks gestation) she weighed 58·7 kg with a height of 145 cm, and at delivery weight was 67·4 kg (36 weeks gestation). Paternal height was 167 cm.

With the commencement of breast-feeding early morning symptoms of hypoglycaemia returned such that breast-feeding had to be discontinued. This was associated with a marked increase in appetite and difficulty in losing weight postpartum. She was referred for surgical treatment. At this stage she weighed 57·2 kg (120% IBW).

The diagnosis of insulinoma was substantiated with fasting blood glucose of 1·6 mmol/l and simultaneous plasma insulin concentrations of 25 mU/l. Skull and chest radiographs were normal, as were measurements of prolactin, growth hormone, cortisol, glucagon, pancreatic polypeptide, neurotensin, VIP and gastrin. Urinary metanephrines concentration was below the limit of detection.

Attempts at pre-operative tumour localization by angiography and abdominal CT scanning failed to demonstrate a tumour. At laparotomy a 1 cm firm nodule was identified in the mid-part of the body of the pancreas and a hemipancreatectomy was performed. Histology confirmed the nodule to be an islet cell tumour and immunoperoxidase staining showed most of the tumour to be positive for insulin with a lesser amount of glucagon and a small amount of alpha-somatostatin. Postoperative recovery was unremarkable. Four months postoperatively she weighed 54·5 kg (114% IBW).

Laboratory findings

Postpartum 12-h metabolic profiles were performed before and 4 months after tumour removal for measurement of insulin, glucose and

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Diabetic Clinic, General Hospital, Birmingham
P. J. HALE *Senior Registrar*
M. NATTRASS *Consultant Physician*

Luton and Dunstable Hospital, Luton
J F. HALE *Consultant Physician*

Correspondence. Dr P. J. Hale, Senior Registrar, The General Hospital, Steelhouse Lane, Birmingham B4 6NH

markers of fat metabolism non-esterified fatty acids (NEFA), glycerol and ketone bodies.

After an overnight fast, blood samples were taken through an indwelling intravenous cannula at 30-min intervals from 08.30 hours (fasting) until 20.00 hours during a normal day with three main meals and two snacks. For each sample 2 ml of whole blood was mixed with 5 ml ice-cold 5% (v/v) perchloric acid and refrigerated immediately for measurement of intermediary metabolites and 5 ml was placed in a lithium heparin tube, centrifuged and plasma stored at −20 °C for measurement of non-esterified fatty acids and insulin.

Blood glucose, lactate, pyruvate, alanine, glycerol and 3-hydroxybutyrate were assayed in the perchloric acid extract by continuous-flow fluorometric methods (Lloyd *et al.* 1978). Acetoacetate was assayed in the perchloric acid extract by a spectrophotometric method (Price *et al.* 1977) within 36 h of sampling. The sum of 3-hydroxybutyrate and acetoacetate concentrations is referred to as total ketone bodies concentration. Non-esterified fatty acids were measured by a radio-cobalt soap method (Turnell *et al.* 1980). Pre-pregnancy insulin concentration was measured by the supra-regional assay service, plasma insulin during metabolic profiles was measured by a double antibody radioimmunoassay method (first antibody—guinea-pig anti-human insulin antibody, Wellcome Reagents Ltd (Beckenham, Kent); second antibody—donkey anti-guinea-pig IgG antibody, Guildhay, University of Guildford, Surrey).

Fasting and 12-h mean values for plasma insulin, blood glucose and intermediary metabolites pre- and 4 months postoperatively are shown in Table 1.

Discussion

The theoretical possibility of endogenous hyperinsulinaemia was postulated by Harris (1924), and within a few years case reports appeared in the literature (Shih-Hao & Hsiao-Chien 1925; Wilder *et al.* 1927; Whipple & Frantz 1935). Spontaneous hypoglycaemia due to insulin secreting pancreatic adenomata is now well recognized although rare with an estimated annual incidence of around 1 per million (Kavlie & White 1972; Frerichs & Creutzfeld 1976). Information on pregnancy in patients with insulinoma is confined to case reports (Cambell *et al.* 1939; Pompen *et al.* 1946; Serrano-Rios *et al.* 1976; Rubens *et al.* 1977; Wilson & Hugh 1983; Osei *et al.* 1984; Shaw *et al.* 1985; Galun *et al.* 1986) (Table 2) and no clear guidelines for management emerge.

In most patients, symptoms, if not diagnosis, pre-dated pregnancy and tended to become more severe with pregnancy necessitating definitive treatment with laparotomy and pancreatic exploration during pregnancy. Amelioration of symptoms with pregnancy has been reported (Cambell *et al.* 1939; Pompén *et al.* 1946), and this was seen in our patient. The first trimester of pregnancy was complicated by marked nausea and vomiting, and in-patient care with elective feeding in the early hours of the morning was advised. With this regimen no symptoms or signs of hypoglycaemia were evident.

The risk of maternal hypoglycaemia to the fetus is not well defined. Meyer (1966) has examined this situation in pregnant psychiatric patients receiving insulin shock treatment and concluded that hypoglycaemia before 10 weeks gestation invariably induced severe malformation and in some cases miscarriage, but after 10 weeks gestation hypoglycaemia had no effect on fetal development. We cannot exclude that the miscarriage which preceded the successful pregnancy was related to hypoglycaemia but it is of interest that fetal histology failed to show any evidence of congenital malformation. Indeed

Table 1. Fasting and 12-h mean concentrations of plasma insulin, blood glucose and intermediary metabolites before and 4 months after removal of an insulinoma

	Plasma insulin (mU/l)	Blood glucose (mmol/l)	Blood lactate (mmol/l)	Blood pyruvate (mmol/l)	Blood alanine (mmol/l)	Blood glycerol (mmol/l)	Blood TKB (mmol/l)	Plasma NEFA (mmol/l)
Fasting								
Before removal	19·8	2·6	1·19	0 051	0·177	0·147	0·097	0·79
Four months after removal	2·4	4·8	1·22	0·042	0·321	0·094	0·071	0·84
Twelve-hour mean								
Before removal	26·3	5·1	1·02	0·059	0·264	0·087	0·069	0·55
Four months after removal	15·5	5·8	1·09	0·048	0·332	0·053	0·077	0·50

Table 2. Previous reports of coincidental insulinoma in pregnancy

Author	Age of patient (years)	Previous uncomplicated pregnancies	Symptoms	Management
Cambell *et al.* (1939)	25	0	Onset in pregnancy, worse with lactation	Postpartum surgery ×2; insulinoma identified at second operation
Cambell *et al.* (1939)	47	1	Started 3 days postpartum; remitted during subsequent pregnancy (miscarriage at 3 months); recurred with *grand mal* seizures; improved with a later pregnancy until 9 months when further seizures occurred; pregnancy terminated and symptoms became more severe	Postpartum surgery; insulinoma identified; residual neurological deficit
Pompen *et al.* (1946)	34	2	Started 13 days postpartum, associated with lactation; improved during subsequent pregnancy and recurred postpartum	Postpartum surgery; insulinoma identified
Serrano-Rios *et al.* (1976)	37	0	Onset 10 months before pregnancy; symptoms complicated by *grand mal* seizure before and during early pregnancy	Surgery at 3 months gestation; multiple insulinoma identified; pregnancy subsequently progressed normally
Rubens *et al.* (1977)	21	0	Present for 2 years before pregnancy but more severe after pregnancy	Surgery at approximately 3 months gestation; insulinoma identified; pregnancy subsequently progressed normally though patient had two further seizures
Wilson & Hugh (1983)	33	2	Onset with pregnancy	Surgery at 17 weeks gestation; insulinoma identified; pregnancy subsequently progressed normally
Osei *et al.* (1984)	19	1	Present for 3 months before surgery	Surgery at 3 months gestation, insulinoma identified; termination of pregnancy
Shaw *et al* (1985)	24	1	Onset at 10 weeks gestation; managed through pregnancy with feeding of complex carbohydrate every 3 h	Postpartum surgery; insulinoma identified
Galun *et al* (1986)	24	0	Onset at 6 weeks gestation; diagnosis made postpartum	Postpartum surgery, insulinoma identified
Present report	41	3	Onset following pregnancy: missed abortion at 11 weeks, symptoms recurred 4 months later but remitted with subsequent pregnancy; recurred with lactation	Postpartum surgery, insulinoma identified

the case reported by Galun *et al.* (1986) suggests that maternal hypoglycaemia throughout pregnancy may not necessarily be harmful to the fetus.

The metabolic profile in our patient post-partum, after the recurrence of symptomatic hypoglycaemia, showed marked fasting hypoglycaemia but near normal 12-h mean glucose concentration. In addition the hyperinsulinaemia, that was evident both fasting and throughout the day, was not associated with suppression of lipolysis or ketogenesis since values for plasma NEFA, and blood glycerol and total ketone bodies concentration were similar before and 4 months after tumour removal. These findings imply that provided fasting hypoglycaemia is avoided there is adequate supply of energy generating substrates. The notable exception to this was the gluconeogenic precursor alanine which was reduced by 45% in the fasted state and by 20% over the 12 h. This may reflect the counter-regulatory effect of increased circulating glucagon concentration (Hayashi *et al.* 1977) which is known to increase hepatic alanine uptake and reduce blood alanine concentration (Malette *et al.* 1969; Felig 1973).

In conclusion this report illustrates that the symptoms of hypoglycaemia in insulinoma may remit with pregnancy, and allow successful outcome with conservative treatment. The post-partum metabolic profiles suggest that management should be directed at the avoidance of fasting hypoglycaemia. Taken in conjunction with previous case reports, it would seem that severity of symptoms remains the major indication for surgical intervention and treatment of insulinoma during pregnancy.

References

Cambell, W. R., Graham, R. R. & Robinson, W. L. (1939) Islet cell tumors of the pancreas *Am J Med Sci* **198**, 445-454.

Felig, P. (1973) The glucose-alanine cycle. *Metabolism* **22**, 179-207.

Frerichs, H. & Creutzfeldt, W. (1976) Hypoglycaemia. 1. Insulin secreting tumours. *Clin Endocrinol Metab* **5(3)**, 747-767.

Galun, E , Ben-Yehuda, A., Berlatzki, J., Ben-Chetrit, E. & Gross, D. J. (1986) Insulinoma complicating pregnancy: Case report and review of the literature. *Am J Obstet Gynecol* **155**, 64-65.

Harris, S. (1924) Hyperinsulinism and dysinsulinism. *JAMA* **83**, 729-733.

Hayashi, M., Floyd, J. C. Jr, Pek, S. & Fajans, S. S. (1977) Insulin, proinsulin, glucagon and gastrin in pancreatic tumors and in plasma of patients with organic hyperinsulinism. *J Clin Endocrinol Metab* **44**, 682-694.

Kavlie, H. & White, T. T. (1972) Pancreatic islet beta cell tumours and hyperplasia: Experience in 14 Seattle hospitals. *Ann Surg* **175**, 326-335.

Lloyd, B., Burrin, J., Smythe, P & Alberti, K G. M M. (1978) Enzymic fluorometric continuous-flow assays for blood glucose, lactate, pyruvate, alanine, glycerol and 3-hydroxybutyrate. *Clin Chem* **24**, 1724-1729.

Malette, L. E., Exton, J H. & Park, C. R. (1969) Effects of glucagon on amino acid transport and utilisation in the perfused rat liver. *J Biol Chem* **244**, 5724-5728.

Meyer, C. M. (1966) The question of hypoglycaemic embryopathy. *Gynaecologia* **161**, 110-115.

Osei, K., Kramer, D. S., Malarkey, W B. & Falko, J. M. (1984) Pregnancy complicated by insulinoma. *Am J Med Sci* **288**, 133-135.

Pompen, A. W. M , Jansen, C. A L. & Dhout, J (1946) Adenoma of the islets of Langerhans and pregnancy. *Acta Med Scand* **124**, 334-347.

Price, C. P., Lloyd, B. & Alberti, K. G. M. M. (1977) A kinetic spectrophotometric assay for rapid determination of acetoacetate in blood. *Clin Chem* **23**, 1893-1897.

Rubens, R., Carlier, A , Thiery, M. & Vermeulen, A. (1977) Pregnancy complicated by insulinoma *Br J Obstet Gynaecol* **84**, 543-547.

Serrano-Rios, M., Cifuentes, I , Prieto, J. C., de Oya, M., Navarro, V. & Marin, G. (1976) Insulinoma in a pregnant woman. *Obstet Gynecol* **47**, 361-364.

Shaw, D. L., Bernene, J L., Williams, J W., North, C. Q & Palestrant, A. M. (1985) Insulinoma in pregnancy. *Ariz Med* **42**, 406-408.

Shih-Hao, L. & Hsiao-Chien, C. (1925) Hypoglycaemia. Report of a case unassociated with insulin administration. *Arch Intern Med* **36**, 146-148.

Turnell, D. C., Price, C. P. & France, M. M. (1980) A ^{57}Co-soap assay for plasma total non-esterified fatty acids compared with a gas-liquid chromatographic method. *Clin Chem* **26**, 1879-1882.

Whipple, A. O. & Frantz, V. K. (1935) Adenoma of islet cells with hyperinsulinism. *Ann Surg* **101**, 1299-1335.

Wilder, R M , Allan, F. N., Power, M. H. & Robertson, H. E. (1927) Carcinoma of the islands of the pancreas. Hyperinsulinism and hypoglycemia. *JAMA* **89**, 348-355.

Wilson, J. D. & Hugh, T. B. (1983) Pregnancy complicated by an insulinoma *Aust NZ J Obstet Gynaecol* **23**, 176-179.

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Maternal death from constrictive pericarditis 15 years after radiotherapy. Case report

S. F. GRAY, M. F. MUERS, J. S. SCOTT

Case report

A 29-year-old primigravid patient had had a large, inoperable mediastinal reticulum cell sarcoma with spinal metastases treated with high-dose radiotherapy and multiple courses of quadruple chemotherapy (vincristine, mustine, procarbazine and prednisone) 15 years previously. She was considered cured. At 27 weeks gestation she was admitted to hospital with a history of cough and blood-streaked green sputum for 3 weeks and pleuritic shoulder tip pain for 12 h. She was mildly dyspnoeic with a blood pressure of 120/80 mmHg There was no evidence of pulmonary embolism on the electrocardiogram. The chest radiograph showed extensive collapse/fibrosis and some cavitation in the right upper lobe, and review of previous films showed some progression of these changes since the 1970s. The changes were attributed initially to the patient's previous radiotherapy. The haemoglobin was 10·3 g/dl and the white cell count $9{\cdot}9\times10^{7}/\mu l$. Pulmonary infection with pleurisy was diagnosed and she was treated with cephradine, but the sputum cultures set up then failed to grow any pathogens.

Her condition did not improve and in a few days signs of right heart failure developed. Small pulmonary emboli were suspected and a restricted perfusion lung scan showed small defects. Intravenous heparin therapy was started. Immediately after this a report was received that acid-alcohol-fast bacilli had been detected in two separate sputum samples, and so antituberculous therapy was commenced. However, her condition continued to deteriorate and 6 days after admission she was more dyspnoeic, the jugular venous pressure was markedly raised, the pulse rate was 110 beats/min and the blood pressure had fallen to 90/60 mmHg. A loud pericardial friction rub became evident. Echocardiography showed some evidence of a thickened pericardium but only a small pericardial effusion. Right ventricular function appeared normal and the appearances were not at that time *typical* of constrictive pericarditis.

The clinical signs suggested constrictive pericarditis, thought probably to be tuberculous in nature. The heparin was stopped because of fear that intrapericardial haemorrhage might aggravate the constriction. The patient was transferred urgently to the Regional Cardiothoracic Unit. A repeat 2-D echocardiogram again confirmed thickened pericardium with some restriction in the movements of the right ventricle. There was also evidence of a thickened endocardium. The appearances were consistent with tuberculous pericarditis.

A limited right cardiac catheterization was performed. This showed a patent superior vena cava. On the atrial pressure tracing there was a steep x/y descent and identical high diastolic pressures (>25 mmHg) in the right atrium, right ventricle and pulmonary artery confirming a diagnosis of constrictive pericarditis.

Despite realization of the risks of the procedure in this case, pericardiectomy was attempted in view of the continued clinical deterioration. At thoracotomy there were dense adhesions over the pericardium and encasing the superior vena cava. On trying to free these, uncontrollable bleeding occurred from the vena cava which proved fatal. An immediate caesarean section was performed but the baby

Clarendon Wing, Leeds General Infirmary, Belmont Grove, Leeds LS2 9NS
SELINA F GRAY *Senior House Officer in Obstetrics*
JAMES S. SCOTT *Professor of Obstetrics and Gynaecology*

Killingbeck Hospital, York Road, Leeds LS14 6UH
MARTIN F. MUERS *Consultant Physician*

Correspondence: Professor J. S. Scott

weighed 1250 g, was in poor condition and survived only 12 h.

Maternal autopsy revealed extensive pericardial fibrosis with fibrinous change and endocardial fibrosis. The right lung had a contracted and solidly fibrosed upper lobe with histological features of interstitial fibrosis and chronic inflammation with giant cells. There were some intrapulmonary thromboses of small arteries. The dense fibrosis extended to the pleura and chest wall at the root of the neck on the right, and encased the superior vena cava. The left lung showed only one small area of fibrosis and acute inflammation in the upper lobe, together with evidence of an early microinfarct in the lower lobe. No evidence of tuberculosis or malignancy was found. The pericardial and endocardial changes were regarded as secondary to radiotherapy, and the lung changes as due to chemotherapy and radiotherapy with superadded microinfarcts. Culture of the sputum produced atypical acid-fast bacilli, identified *post mortem* as belonging to the Avium-intracellulare-scrofulaceum group of opportunistic mycobacteria; this was confirmed on a duplicate slope.

Death was attributed to the combination of pregnancy and the effects of the treatment of the malignant tumour 15 years previously.

Discussion

Relatively young patients now have a much improved prospect of survival following aggressive treatment of certain malignant conditions. Such women may then seek advice regarding possible problems with childbearing. These have been reviewed by Barber (1981) and, provided ovulation has been shown to be occurring regularly, the outlook for achieving pregnancy and completing it successfully is surprisingly good in most cases. However, a particular, but little known, risk exists when pregnancy occurs in women who have had thoracic radiation. The resulting fibrosis may cause pericardial constriction (Stewart & Fajardo 1984) which may precipitate circulatory failure with the cardiac expansion induced by a pregnancy. In our patient such an effect proved fatal 14 years after the treatment.

Certain agents used in cancer chemotherapy are cardiotoxic, particularly doxorubicin (Kantrowitz & Bristow 1984), and this may contribute. The pericarditis which may develop as a complication of mediastinal radiotherapy (Stewart & Fajardo 1984) is dose related and may present with immediate acute inflammation and effusion or as late constrictive disease. Cases have been reported presenting as long as 17 years (Scott & Thomas 1978) and 45 years (Haas 1969) after treatment. This late form is the more serious and is frequently associated with endocardial or myocardial fibrosis. Once signs of constriction develop the outcome may be rapidly fatal (Coltart *et al.* 1985). Pericardectomy is the treatment of choice, but associated cardiac fibrosis can reduce the prospect of it being successful. Very dense retrosternal and pericardial adhesions may make the operation hazardous but pregnancy itself is not a contraindication.

Richardson *et al.* (1970) reported a patient with tuberculous pericarditis who had a successful pericardectomy at 24 weeks gestation. Another 20-year-old patient had an uncomplicated pericardectomy performed at 32 weeks gestation (Watson *et al.* 1980). She had been treated with radiotherapy for Hodgkin's disease 6 years previously. This had been given to affected cervical and axillary nodes, as well as to spleen and aortic nodes but not directly to the mediastinum. She gave birth to a healthy live infant shortly after the operation.

The unsuccessful outcome in our patient was probably related to the large dose of direct mediastinal radiotherapy and the precise site and extent of the original growth. The note on the original thoracotomy indicated that the tumour was extremely large, infiltrating the pericardium, sternum and chest wall and compressing the superior vena cava. The very dense fibrosis surrounding the superior vena cava was presumably due to resolution of the malignant tissue. The additional load on the cardiovascular system posed by pregnancy with consequent increased cardiac volume precipitated the effects of acute pericardial constriction. These were aggravated by respiratory infection and/or pulmonary micro-emboli. In retrospect it seems that the finding of acid-alcohol-fast bacilli in the sputum was merely a confusing factor as the bacilli cultured were eventually identified as belonging to an opportunistic group of organisms.

It is clearly the case that patients who have had mediastinal radiotherapy and who achieve pregnancy run the risk of radiation-induced pericardial constriction presenting as a serious problem even many years after radiation. This should be taken into consideration when counselling such patients concerning pregnancy. Once pregnant, they need careful cardiovascular assessment and monitoring. The risks of operation to relieve the constriction are probably not specific to pregnancy and relate to the intrathoracic pathology.

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References

Barber, H. R. K. (1981) The effect of cancer and its therapy upon fertility. *Int J Fertil* **26**, 250-259.

Coltart, R. S., Roberts, J T., Thom, C. H. & Petch, M. C. (1985) Severe constrictive pericarditis after single 16MeV anterior mantle irradiation for Hodgkin's disease. *Lancet* **i**, 488-489.

Haas, J. M (1969) Symptomatic constrictive pericarditis 45 years after radiation therapy to the mediastinum. *Am Heart J* **77**, 89-95.

Kantrowitz, N. E. & Bristow, M. R. (1984) Cardiotoxicity of antitumour agents. *Prog Cardiovasc Dis* **27**, 195-200

Richardson, P. M., Le Roux, B T., Rogers, N. M. A. & Gotsman, M. S. (1970) Pericardiectomy in pregnancy. *Thorax* **25**, 627-630.

Scott, D L. & Thomas, R. D (1978) Late onset constrictive pericarditis after thoracic radiotherapy *Br Med J* **i**, 341-342.

Stewart, J R. & Fajardo, L F. (1984) Radiation-induced heart disease: an update *Prog Cardiovasc Dis* **27**, 173-194.

Watson, P T., Havelda, C J., Sorosky, J., Kochenour, N. K., Sohi, G. S. & Gray, L. (1980) Irradiation-induced constrictive pericarditis requiring pericardiectomy during pregnancy. *J Reprod Med* **24**, 127-130

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Pre-operative treatment of an abdominal wall endometrioma with nafarelin acetate. Case report

S. H. KENNEDY, J. BRODRIBB, A. M. GODFREY, D. H. BARLOW

Case report

A 27-year-old woman presented with an abdominal wall endometrioma and secondary infertility. She complained of dysmenorrhoea, deep dyspareunia and cyclical lower abdominal pain. She last used the combined oral contraceptive 2 years earlier.

In 1977, at another hospital, she had an abdominal hysterotomy for termination of a 14-week pregnancy. She presented in 1978 with abdominal pain of uncertain origin. A tender abdominal scar nodule was noted in 1981 and excised in 1983; histology showed endometriosis. Although the area healed well it became painful again in 1984. She wanted to conceive but was anovulatory. She took clomiphene which exacerbated her symptoms so that, in 1985, she was given danazol 200 mg three times daily, but for only 3 months because of severe side-effects.

On examination, in 1986, there was a tender mass, 7·5 cm in diameter, above her Pfannenstiel incision. The pelvis was tender and the pouch of Douglas indurated. She started taking intranasal nafarelin acetate 200 μg twice daily and was amenorrhoeic thereafter. Within 1 month her symptoms were improving; oestradiol levels were in the menopausal range (<70 pmol/l) and she was having daily hot flushes which were well tolerated. After 6 months treatment, the lesion was the same size and still tender. Computer-assisted tomography showed the lesion to be 7·5 cm in diameter and 2·5 cm deep, involving the entire depth of the anterior abdominal wall (Fig. 1). She had significant continuing pain and after lengthy discussion she opted for excision of the lesion with plastic surgery to reconstruct the abdominal wall.

At operation, a vertical skin elipse was incised with 3 cm clearance of the involved skin. The incision was deepened shelving laterally to clear the palpable mass continuing through subcutaneous fat, fascia, muscle and peritoneum. An area of adherent omentum beneath the mass was excised in continuity with the main specimen (Fig. 2). A few small deposits of endometriosis in the pouch of Douglas were cauterized; the pelvis was otherwise free of disease. Reconstruction was carried out using a turn-down flap of the upper right anterior rectus sheath reinforced by a nylon darn. Subcutaneous tissue and skin were then closed as a single vertical left paramedian scar. The lesion was a 7 × 7 × 5 cm mass of connective tissue with blood-filled cavities; histology showed evidence of recent haemorrhage and mitotic activity in some endometrial glands.

Three months after surgery she was symptom free and the wound well healed. Advised against pregnancy in the short term she was using the combined oral contraceptive continuously.

Discussion

This is the first recorded case of treatment of an abdominal wall endometrioma with a luteinizing hormone-releasing hormone (LHRH) analogue. Nafarelin acetate, [D-Nal (2)^6] LHRH, is an LHRH agonist over 200 times more potent than native LHRH (Nestor 1984). Long-term

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Nuffield Department of Obstetrics and Gynaecology, John Radcliffe Hospital, Headington, Oxford
S. H KENNEDY *Research Fellow*
J. BRODRIBB* *Research Fellow*
D. H. BARLOW *Clinical Reader*

Department of Plastic Surgery, Radcliffe Infirmary, Oxford
A M. GODFREY *Consultant Surgeon*

Correspondence: S. H. Kennedy, Nuffield Department of Obstetrics and Gynaecology, John Radcliffe Hospital, Oxford
*Present address: J Brodribb, Odstock Hospital, Salisbury

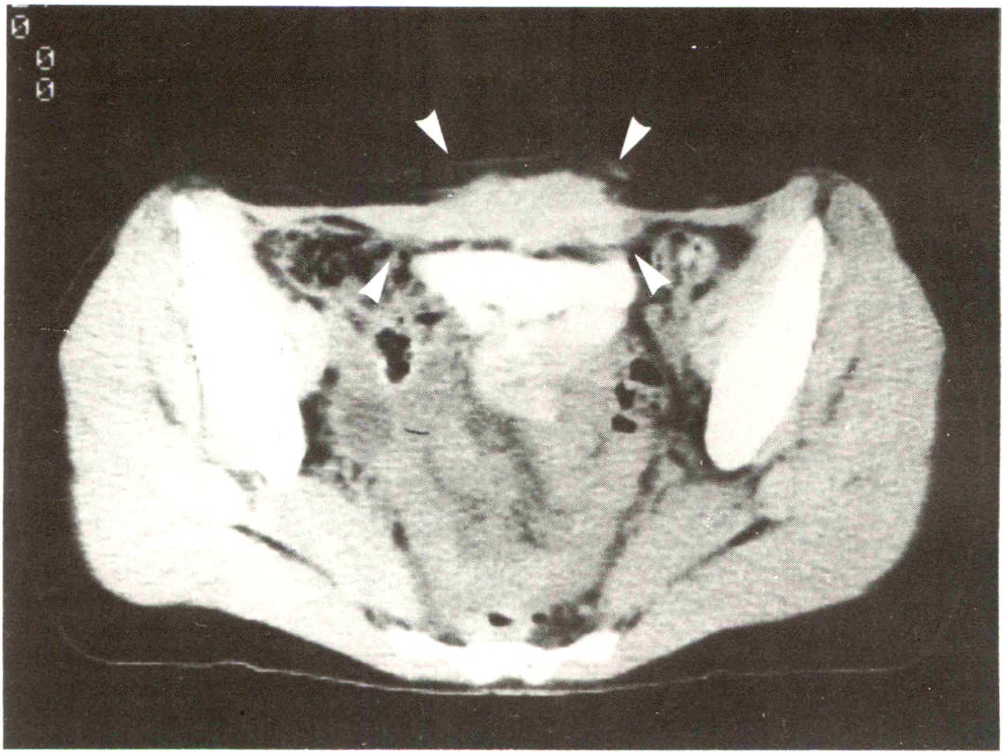

Fig. 1. CT scan of abdominal wall endometrioma.

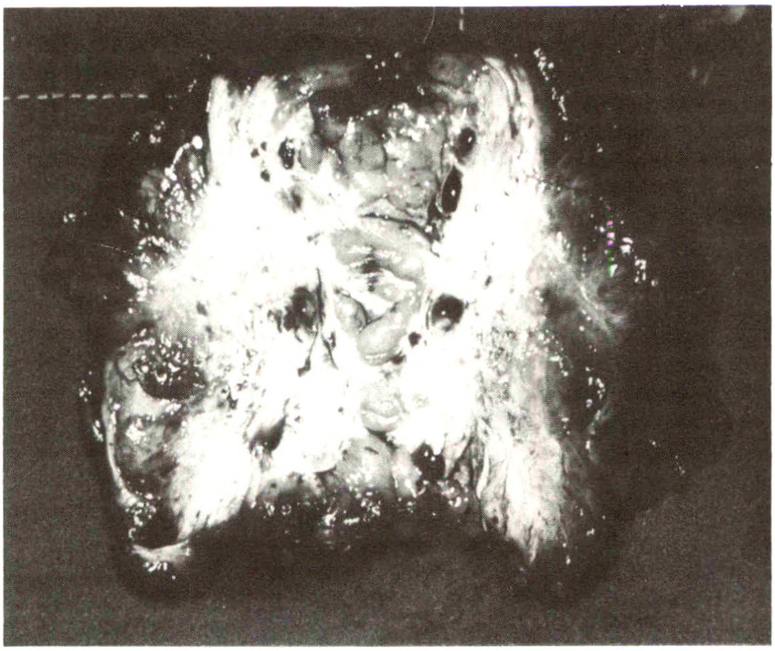

Fig. 2. Photograph of specimen.

agonist administration induces a reversible hypogonadotrophic pseudomenopause by pituitary down-regulation (Rabin & McNeil 1980). As oophorectomy is effective treatment for endometriosis, analogues are being assessed for their efficacy. Preliminary results from a multicentre trial show that danazol and intranasal nafarelin acetate improve symptoms and resolve endometriotic implants equally well (Henzl *et al.* 1986), but there is little evidence that medical treatment reduces pelvic endometriomata. Schriock *et al.* (1985) found a 6 cm ovarian endometrioma hardly changed after 6 months treatment with nafarelin acetate. In our patient, effective abolition of ovarian follicular activity failed to reduce the size of the endometrioma and left mitotic activity within some endometrial glands.

Scar endometriosis caused by surgical implantation of endometrial tissue is rare. It occurs experimentally if menstrual endometrium is injected into a woman's abdominal wall (Ridley & Edwards 1958); after episiotomy (Paull & Tedeschi 1972), puerperal sterilization (Chatterjee 1980), reversal of sterilization (McKenna & Wade-Evans 1985), inguinal herniorrhaphy (Steck & Helwig 1965) and appendicectomy (Jones & Jones 1975). It occurs most commonly after uterine surgery, with a frequency of 1·08% (12/1129) after mid-trimester abdominal hysterotomy and 0·03% (1/3736) after caesarean section (Chatterjee 1980). Endometroid carcinoma in an abdominal wall endometrioma has been described (Madsen *et al.* 1980).

The risk after mid-trimester hysterotomy is eliminated if the uterus is incised outside the abdomen without spillage (Martin & Higginbottom 1973). The interval between surgery and clinical presentation can be 1–37 years (McKenna & Wade-Evans 1985). The diagnosis is usually apparent clinically; abdominal lesions have been diagnosed with ultrasound (Miller & Melson 1979) and computer-assisted tomography (Amato & Levitt 1984).

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References

Amato, M. & Levitt, R. (1984) Abdominal wall endometrioma: CT findings. *J Comput Assist Tomogr* **8**, 1213-1214.

Chatterjee, S. K. (1980) Scar endometriosis: A clinicopathologic study of 17 cases. *Obstet Gynecol* **56**, 81-84.

Henzl, M., Monroe, S., Corson, S. & Moghissi, K. S. (1986) Management of endometriosis with nasal dosing of nafarelin. In *Program and Abstracts, 68th Annual Meeting, The Endocrine Society*, p. 37.

Jones, H. W. & Jones, J. J. (1975) *Novak's Textbook of Gynaecology*. Williams & Wilkins, Baltimore, London, p. 662.

McKenna, P. & Wade-Evans, T. (1985) Anterior abdominal wall endometriosis. *J Obstet Gynaecol* **6**, 114-116.

Madsen, H., Hansen, P. & Anderson, O. P. (1980) Endometroid carcinoma in an operation scar. *Acta Obstet Gynecol Scand* **59**, 475-476.

Martin, R.H. & Higginbottom, J. (1973) Hysterotomy and endometriosis. *Lancet* **ii**, 106.

Miller, W. B. & Melson, G. L. (1979) Abdominal wall endometrioma. *J Radiol* **132**, 467-468.

Nestor, J. J. (1984) Development of agonistic LHRH analogs. In *LH-RH and its Analogs* (Vickery, B. H., Nestor, J. J. & Hafez, E. S. E., eds), MTP Press, Lancaster.

Paull, T. & Tedeschi, L. G. (1972) Perineal endometriosis at the site of episiotomy scar. *Obstet Gynecol* **40**, 28-34.

Rabin, D. & McNeil, L. W. (1980) Pituitary and gonadal desensitisation after continuous luteinizing hormone-releasing hormone infusion in normal females. *J Clin Endocrinol Metab* **51**, 873-876.

Ridley, J. H. & Edwards, K. (1958) Experimental endometriosis in the human. *Am J Obstet Gynecol* **76**, 783-790.

Schriock, E. D., Monroe, S. E., Henzi, M. & Jaffe, R. B. (1985) Treatment of endometriosis with a potent agonist of gonadotrophin-releasing hormone (Nafarelin). *Fertil Steril* **44**, 583-588.

Steck, W. D. & Helwig, E. B. (1965) Cutaneous endometriosis. *JAMA* **191**, 167-170.

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Adenomatoid tumour of uterus. Case report

CLAUS CHRISTENSEN, PETER BICHEL

Case report

A 25-year-old woman was admitted for exploration of a uterine tumour, which was revealed by ultrasonic echograms. Menarche occurred at age 14, and menstrual cycles were regular, 6/28 days. She did not use any contraception and had never been pregnant.

At the age of 16 years she had undergone surgical treatment with removal of a 7-cm large intraligamentous paraovarian cyst. The histological examination revealed a serous cyst without signs of malignancy. At the same time the lateral part of the left uterine tube was removed, as it was impossible to separate it from the cyst.

At the age of 17 and 18 years she had undergone laparatomy with puncture of left- and right-sided benign ovarian cysts, respectively. At the last laparatomy the left ovary appeared normal and the uterus was retroflexed and normal in size. Since then, until admission, she had no gynaecological problems.

She was admitted because of pain in the lower abdomen radiating to the back, in particular from 3 to 4 days before start of menstruation, and lasting 8–10 days, and again 3–4 days around the time of ovulation. During the last two periods the pain had been constant during the whole cycle. Gynaecological examination revealed an enlarged retroflexed uterus which was soft in consistency, and slightly tender, but otherwise normal. On the basis of this and ultrasonic echograms myomectomy was indicated.

Laboratory examinations

Haemoglobin, 13·37 g/dl. Sedimentation rate, 2 mm/h. Serum creatinine, 67 μmol/l.

During operation a few millilitres of blood-stained serous liquid were found in the peritoneal cavity, but there were no tumour cells. The uterus was mobile and an area including the fundus and most of the posterior wall was transformed to a poorly demarcated intramural, partly cystic tumour. The right ovary was normal. The left ovary contained a few cysts, which were punctured. The uterine tubes were transformed to 1·5 cm thick hydrosalpinges.

A 5×5×3 cm, poorly demarcated tumour was removed. During this procedure a great deal of liquid oozed from the tumour, in which no tumour cells were revealed at cytological examination. Cryostat sections showed microglandular tumour tissue judged to be a benign adenomatoid tumour.

Since the wall of the fundus and most of the posterior part of the uterus were considerably deformed by the infiltrating tumour, and since there was bilateral hydrosalpinx, it was decided to perform hysterectomy and bilateral salpingectomy.

The postoperative period was uncomplicated.

Pathological findings

Gross. The tumour received for cryostat investigation was removed from the fundus and measured 5×5×3 cm; it was greyish, rather homogeneous and elastic in consistency. The uterus measured 11×8×4 cm with a myometrial wall of about 2·5 cm, and weighing 152 g after the tumour was removed. The biopsy cavity opened broadly to the peritoneum, but in the wall of the cavity there was a tumour residue of 0·5–1·5 cm in thickness. Thus the total size of the tumour was about 6 cm in diameter.

Microscopy. The tumour was composed of small

Department of Obstetrics and Gynecology, Kolding Central Hospital, Denmark
CLAUS CHRISTENSEN

Institute of Pathology, Vejle Central Hospital, Denmark
PETER BICHEL

Correspondence: Claus Christensen, Skovbrynet 22, DK-6000 Kolding, Denmark

and medium-sized more or less gland-like structures separated by scanty rather loose connective tissue stroma (Fig. 1), intermingled at the periphery with the fibres of the surrounding myometrium. The glands were covered by a one-layer cubic epithelium with brush border. The cells were large, rich in eosinophilic and PAS-positive cytoplasm and contained medium-sized round or oval nuclei without conspicuous nucleoli. There was no mitosis and no signs of malignancy. The histological picture was considered characteristic for an adenomatoid tumour.

Discussion

The adenomatoid tumour is a rare benign genital tract neoplasm. Golden & Ash (1945) described it for the first time and proposed the term 'adenomatoid tumour' for certain distinctive neoplasms of the genital tract, described previously under a variety of terms, including lymphangioma, adenomyoma, reticuloendothelioma, angiomatoid tumour, adenofibroma, adenoma, and mesothelioma. They favoured the term adenomatoid tumour as being 'morphologically correct and genetically neutral'. The growing body of evidence now seems to favour a mesothelial origin for these lesions (Stephenson & Mills 1986; Suzuki *et al.* 1985).

Most reported examples have occurred in male patients, usually at the lower pole of the epididymis, but also in the caput of the epididymis, testis, and testicular tunica. In female patients they occur in the uterus beneath the serosa in the cornual region and in the fallopian tubes with nearly equal frequency, and occasionally in the ovary and paraovarium (Williamson & Moore 1964; Tiltman 1980).

The tumours are rarely more than 0·5–2·0 cm in greatest dimension (Tiltman 1980), and are usually incidental findings at the time of hysterectomy, being grossly similar to leiomyomas. This similarity, however, probably does not account for the infrequency of discovery, for even under enlightened scrutiny only 12 cases over a 7-year period were collected from 8000 hysterectomies and 300 myomectomies (Lee *et al.* 1950).

Youngs & Taylor (1967) reported 29 women with adenomatoid tumour, 13 of the uterus and 16 of the fallopian tube. At the time of diagnosis, the age of the patients ranged from 30 to 72 years (median 42 years). There was no evidence of

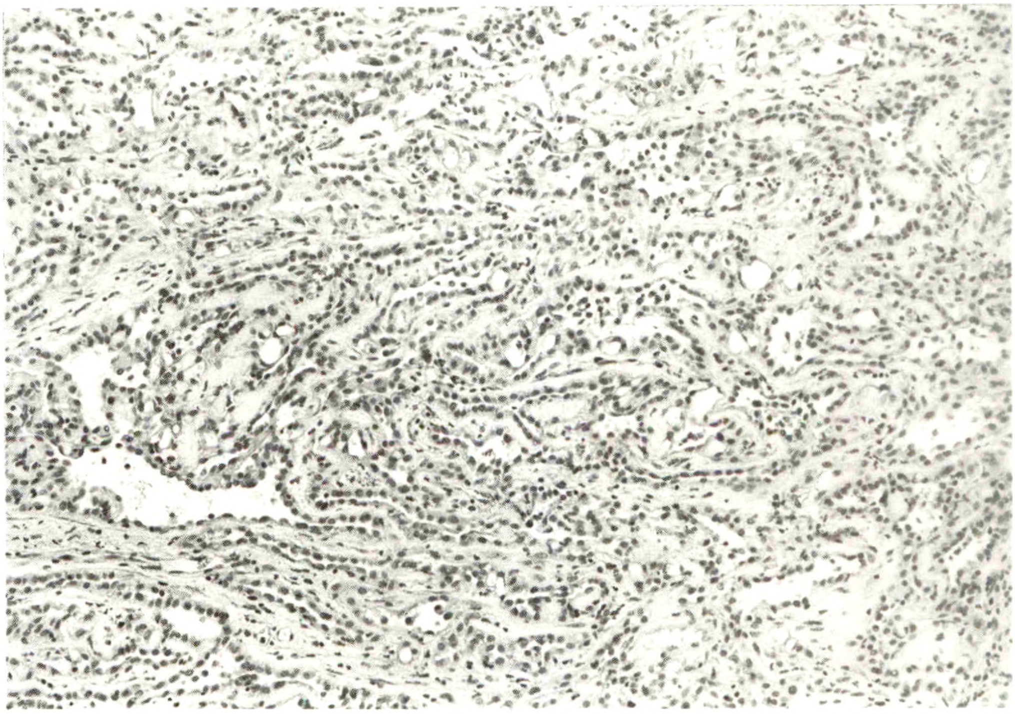

Fig. 1. Adenomatoid tumour composed of irregular glands covered with a rather monotonous one-layer cubic epithelium without atypia. Haematoxylin and eosin. ×120.

impaired fertility. There was no racial predilection. Follow-up information was obtained from 17 patients at 6 months–22 years (mean 9 years) after diagnosis. None of these patients had any evidence of recurrent or metastatic tumour. Uterine leiomyomas were found in 59% of the patients in the study. The common association of uterine leiomyomas with adenomatoid tumours has been noted by Honore & O'Hara (1979) who reported a frequency of 80%, and this is probably explained by the frequency of myomas and the comparable age distribution of these lesions. Furthermore, many of these patients were operated upon for myomas, and the discovery of the adenomatoid tumour was incidental. In contrast to leiomyomas, adenomatoid tumours are rarely multiple. Youngs & Taylor (1967) reported the first two tumours located in the female genital tract.

Simple excision is the treatment of choice, for recurrence has not been documented, and 'malignant degeneration' is rare (Fisher & Klieger 1966), although a malignant variant has been described by Teilum (1954).

The tumour described here was remarkable in the following respects: first, the tumour, which was located in the wall of fundus and most of the posterior part of uterus, was so large that it was noticed at gynaecological examination, and necessitated hysterectomy. Second, the patient was only 25 years of age, and this tumour is most frequently seen in an older age group. Third, this patient did not have an accompanying leiomyoma, which is seen in patients with adenomatoid tumours with great frequency, ranging from 59% to 80% (Youngs & Taylor 1967; Honore & O'Hara 1979).

References

Fisher, E. R. & Klieger, H. (1966) Epididymal carcinoma (malignant adenomatoid tumour, mesonephric, mesodermal carcinoma of epididymis). *J Urol* **95,** 568-572.

Golden, A. & Ash, J. E. (1945) Adenomatoid tumours of the genital tract. *Am J Pathol* **21,** 63-79.

Honore, L. H. & O'Hara, K. E. (1979) Adenomatoid tumour of the fimbrial endosalpinx: report of two cases with discussion of histogenesis. *Eur J Obstet Gynecol Reprod Biol* **9,** 335-339.

Lee, M. J., Dockerty, M. B., Thompson, G. J. & Waugh, J. M. (1950) Benign mesotheliomas (adenomatoid tumours) of the genital tract. *Surg Gynecol Obstet* **91,** 221-231.

Stephenson, T. J. & Mills, P. M. (1986) Adenomatoid tumours: an immunohistochemical and ultrastructural appraisal of their histogenesis. *J Pathol* **148,** 327-335.

Suzuki, T., Yoshida, Y., Kaku, T., Kikuchi, K. & Mori, M. (1985) Adenomatoid tumour of the uterus. Ultrastructural, histochemical, and immunohistochemical analyses. *Arch Pathol Lab Med* **109,** 1049-1051.

Teilum, G. (1954) Histogenesis and classification of mesonephric tumours of the female and male genital system and relationship to benign so-called adenomatoid tumours (mesotheliomas)—a comparative histological analysis. *Acta Pathol Microbiol Scand* **34,** 431-481.

Tiltman, A. J. (1980) Adenomatoid tumours of the uterus. *Histopathology* **4,** 437-443.

Williamson, H. O. & Moore, M. P. (1964) Ovarium and paraovarian adenomatoid tumours. Case reports. *Am J Obstet Gynecol* **90,** 388-390.

Youngs, L. A. & Taylor, H. B. (1967) Adenomatoid tumours of the uterus and fallopian tube. *Am J Clin Pathol* **48,** 537-545.

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Mucinous cystadenocarcinoma in pregnancy. Case report

T. VAN DESSEL, T. M. HAMEETEMAN, Sj. Sc. WAGENAAR

Case report

A 36-year-old white European woman, gravida 4, para 3, was referred to our hospital at 17 weeks gestation. Previous medical and obstetric history was unremarkable. Bimanual pelvic examination revealed a large mass arising from the right adnexa. Ultrasound scan showed a normal fetus with biparietal diameter just below the 50th centile. There were no apparent malformations. A large multiple cystic mass was visible in the right lower quadrant of the abdomen. Laboratory studies, including hormone assays, were normal.

Laparotomy was undertaken which showed a cystic mass in the right ovary, about 12 cm in diameter. Right oophorectomy was performed. Histological examination of a frozen section of the right ovary revealed malignancy. The left ovary, liver and omentum were grossly normal. There was no apparent increase in peritoneal fluid. Peritoneal washings for cytology were done. Examination of the collected fluid showed no malignant cells.

The carcinoma seemed to be confined to the right ovary and no evidence of metastatic disease was found. The operation was therefore limited to right oophorectomy. Definitive surgical staging, including hysterectomy and left salpingo-oophorectomy, was planned after delivery.

Histological examination revealed a well-differentiated mucinous cystadenocarcinoma (Fig. 1). The capsule of the ovary was intact. The diagnosis was therefore: mucinous cystadenocarcinoma of the right ovary, Stage IA, grade I.

The postoperative course was uneventful.

In the course of following antenatal attendances a progressive fetal growth retardation was seen (Fig. 2). The diastolic blood pressure was normal (75 mmHg). Laboratory studies showed normal kidney and liver functions. Coagulation studies were normal. Intrauterine fetal death was established at 29 weeks.

Labour was induced by prostaglandin infusion (sulproston). A macerated female fetus of 600 g was born. Autopsy, including microscopic examination, did not offer an explanation for the unfortunate fetal outcome.

The placenta weighed 110 g. Histological examination of the placenta revealed 15% infarctions, but no metastases. Studies for bacterial or viral infections of placenta and fetus were normal.

Surgical staging was refused by our patient. She is now, 18 months after the operation, in good health without signs of metastatic disease.

Comment

Carcinomas of the ovary have very rarely been diagnosed during pregnancy. The reported incidences vary from one in 12 000 (White 1973) to one in 50 000 (Betson & Golden 1958) with an average of 1 in 25 000. In an 80-year review of the world literature, Jubb (1963) found 34 cases of primary ovarian cancer associated with pregnancy, of which 12 (34%) were serous and 7 (20%) mucinous cystadenocarcinoma. In a detailed study of the literature since then, we could identify 22 additional cases of which 12 (55%) were serous and 4 (18%) mucinous carcinoma (Beischer *et al.* 1971; Chung 1973;

Department of Gynaecology and Obstetrics, Westeinde Hospital, Lijnbaan 32, 2501 CK Den Haag, The Netherlands
T. VAN DESSEL

St Antonius Hospital, Koekoekslaan 1, 3435 CM Nieuwegein, The Netherlands
Department of Gynaecology and Obstetrics
T. M. HAMEETEMAN

Department of Pathology
Sj. Sc. WAGENAAR

Correspondence: T. van Dessel

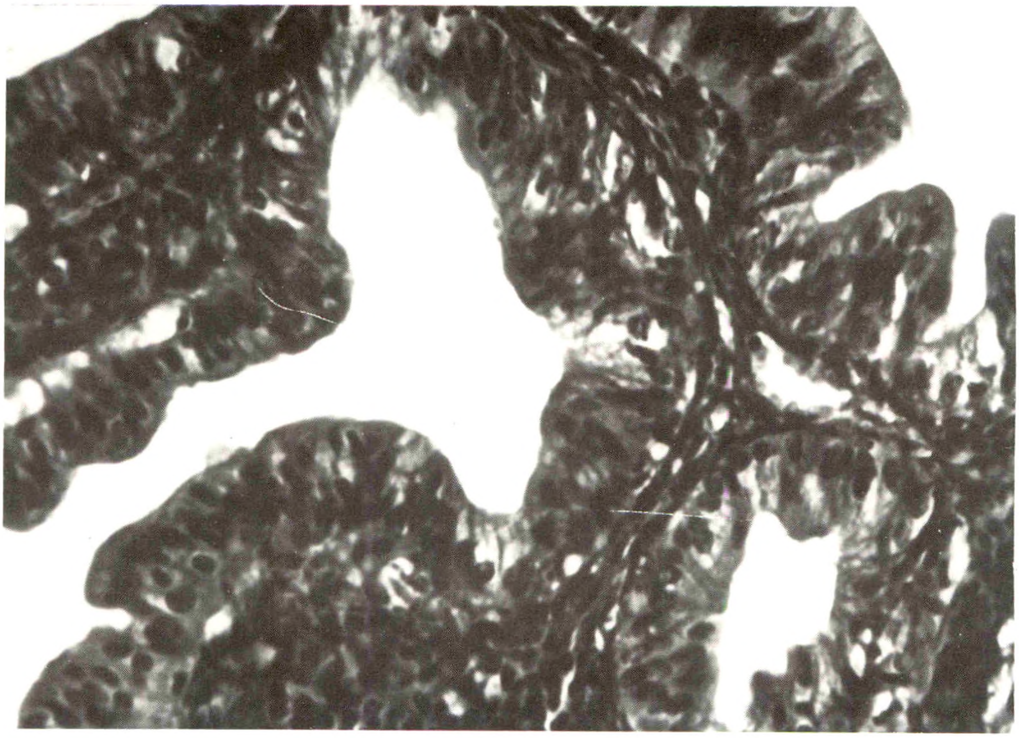

Fig. 1. Mucinous cystadenocarcinoma of the right ovary.

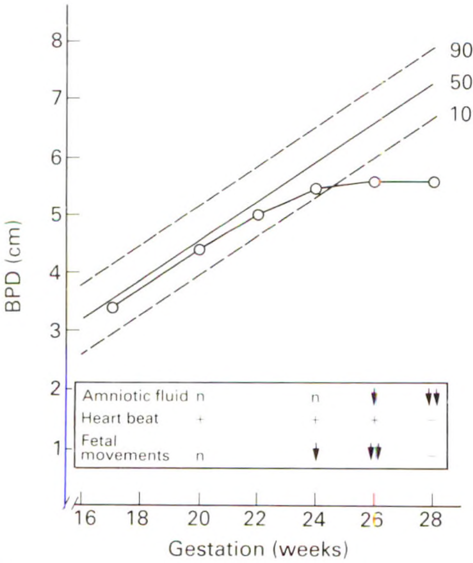

Fig. 2. Biparietal diameter (BPD) between 16 and 28 weeks gestation (○——○), quantity of amniotic fluid, heart beat and fetal movements. n, Normal; ↓ decreased; +, positive; −, negative. The dotted lines show the 90th, 50th and 10th centile values.

Cruikshrank *et al.* 1982; Novak *et al.* 1975). To conclude, the estimated frequency of mucinous cystadenocarcinoma in pregnancy is one in approximately 125 000. Most mucinous tumours occur in women over 35 years of age (Woodruff *et al.* 1978), which might explain their rarity in pregnancy. Sometimes the diagnosis is made during caesarean section (Ahram *et al.* 1985). In other cases the tumour became symptomatic after torsion or rupture. The diagnosis is only occasionally made in an asymptomatic woman.

The present case was complicated by progressive fetal growth retardation and intrauterine fetal death. No similar cases have been recorded in the literature. When oophorectomy was performed before 16 weeks gestation no unfavourable fetal outcome was reported (Jubb 1963). We found only six patients, operated on after 16 weeks, and two of them had an intrauterine death immediately after operation.

Treatment in Stage IA disease should be unilateral oophorectomy (Munnell 1963), followed by pelvic clean-out after delivery or observation. More advanced stages need more radical treatment.

Whether there is a relation between the

(removal of the) tumour and the fetal complications remains obscure. Haemodynamic changes in uterine flow after operation or immunological changes caused by the tumour might explain the progressive fetal growth retardation, resulting in fetal death

References

Ahram, J , Lakoff, K & Miller, R (1985) Serous cystadenocarcinoma as incidental finding during a repeat ceasarean section *Am J Obstet Gynecol* **153,** 78-79

Betson, J R & Golden, M. L. (1958) Primary carcinoma of the ovary coexisting with pregnancy *Obstet Gynecol* **12,** 589-595

Beischer, N. A , Buttery, B W , Fortune, D W & Macafee, C A. J (1971) Growth and malignancy of ovarian tumours in pregnancy *Aust NZ J Obstet Gynaecol* **11,** 208-220.

Chung, A. (1973) Ovarian cancer associated with pregnancy *Obstet Gynecol* **41,** 211-214

Cruikshrank, S H , McNeillis, T. M & Wise, H. D (1982) Mucinous cystadenocarcinoma of the ovary associated with pregnancy *Mo Med* **79,** 695-703

Jubb, E D. (1963) Primary ovarian carcinoma in pregnancy. *Am J Obstet Gynecol* **85,** 345-354

Munnell, E. W (1963) Primary ovarian cancer associated with pregnancy *Clin Obstet Gynecol* **6,** 983-993

Novak, E. R , Lambrou, C D. & Woodruff, J D. (1975) Ovarian tumors in pregnancy *Obstet Gynecol* **46,** 401-406.

White, K. C (1973) Ovarian tumors in pregnancy *Am J Obstet Gynecol* **116,** 544-550

Woodruff, J. D., Perry, H , Genadry, R & Parmley, T. (1978) Mucinous cystadenocarcinoma of the ovary *Obstet Gynecol* **51,** 483-489

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Recovery of the intrauterine contraceptive device from the sigmoid colon. Three case reports

J. J. BROWNING, M. A. BIGRIGG

Case reports

Patient no. 1

A 24-year-old woman attended the surgical outpatient department. She complained of episodic right upper quadrant abdominal pain for 1 year, associated with fat intolerance.

Because of vague lower abdominal pain and two coliform urinary tract infections, the patient's general practitioner had ordered an excretion urogram. The plain films indicated multiple radio-opaque stones in the right upper quadrant, and an intrauterine contraceptive device (IUCD) in the left side of the abdominal cavity. The urogram was normal and indicated the stones to be extrarenal. Biliary ultrasound confirmed multiple gall bladder stones. Inquiry revealed that she had five children, the first three by normal vaginal delivery, and after which an IUCD had been inserted in 1980. Two subsequent deliveries had been by lower segment caesarean section: the first was for unstable lie and the second for breech presentation. The latter was accompanied by tubal ligation. The IUCD had never been recovered.

The patient underwent laparotomy. Through a midline incision a cholecystectomy was performed with exploration of the common bile duct and T-tube insertion. The IUCD was palpated in the mid sigmoid colon. A colotomy was performed, and a Copper-7 device lying 80% in the gut lumen was removed, with primary bowel repair.

She made an uneventful recovery.

Patient no. 2

A 31-year-old woman was seen in the gynaecology clinic at 10 weeks gestation in her fourth pregnancy. An IUCD inserted painlessly 2 years previously had failed, and this pregnancy was unwanted.

She therefore underwent suction termination of pregnancy. Despite thorough uterine exploration, the device was not removed.

Ultrasound scan confirmed the extrauterine position of the IUCD. Plain films indicated it to be in the left hemipelvis. By now she had noticed a constant left iliac fossa ache.

The IUCD could not be seen at laparoscopy; greater omentum was adherent to the rectosigmoid junction, so laparotomy was performed through a Pfannenstiel incision. After dissection of the omentum, a Copper-T coil was seen to have eroded through the full thickness of bowel wall. After a small colotomy it was removed. The defect was closed and oversewn with omentum. The patient made a good postoperative recovery and was discharged home on the third day.

Patient no. 3

A 37-year-old woman had five babies by normal vaginal delivery at term. She had conceived with an IUCD *in situ*. It had not been recovered.

She was urgently admitted with a septic miscarriage at 19 weeks gestation. After resuscitation, she was given intravenous gentamicin, cefuroxime and metronidazole. (Blood cultures later yielded growth of *Escherichia coli*.) Labour

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Department of Obstetrics and Gynaecology, John Radcliffe Hospital, Oxford OX3 9DU
J. J. BROWNING *Registrar*

Department of Surgery, Princess Margaret Hospital, Swindon SN1 4JU
M. A. BIGRIGG *Registrar*

Correspondence: J. J. Browning, Department of Obstetrics and Gynaecology, Bristol Maternity Hospital, Bristol BS2 8EG

was augmented by intravenous oxytocin. The products of conception appeared complete, but the IUCD was not expelled. She had a persistent pyrexia and tachycardia. Her abdominal pain worsened and peritonitis was now evident. She therefore underwent emergency laparotomy and subtotal hysterectomy. A Copper-T device had perforated the posterior uterine wall and had eroded into the serosa of the sigmoid colon. It was removed but the defect was not repaired.

A stormy postoperative course was complicated by pulmonary embolism requiring heparinization, and cardiac failure necessitating inotropic support. The patient developed increasing abdominal pain. Serial chest X-rays showed increasing subphrenic air, and a gastrograffin enema demonstrated a sigmoid colonic leak.

Laparotomy was performed 48 h after the first operation: the colonic leak was closed and oversewn with omentum. A transverse colostomy was fashioned. The patient made a gradual recovery and was discharged home. She is due to have her colostomy reversed.

Discussion

In two of our patients the IUCD was retrieved electively and in the third the operation was performed as an emergency. In two patients, pregnancy had occurred after translocation of the device.

Almost half a million women use the IUCD in the UK (Smith *et al.* 1983). Perforation probably occurs in about 1 in 1000 insertions. It is related to operator inexperience (Tietze & Lewit 1970) and the insertion of the device in the lactating woman (Heartwell & Schlesselman 1983). Death occurs in 1–20 women per million users per year (Anonymous 1982; Siddle 1984) and is usually associated with infection, with or without perforation.

Gastrointestinal complications arise when perforation occurs through the uterine wall, and the IUCD becomes intraperitoneal. In the British literature, small bowel infarction has been described, due to strangulation by the thread (Smith *et al.* 1983). IUCD-associated 'appendicitis' has been reported (Key & Kreutner 1980; Bromham 1981; Goldman *et al.* 1983). Case reports of large bowel perforation include three in the sigmoid colon (Key & Kreutner 1980) and four in the rectum (Key & Kreutner 1980; Abdalla 1984; Bromham *et al.* 1984; Haloob 1986). Spontaneous passage of the device (Tushuizen & Ubachs 1973; Ismail 1977) and proctosigmoidoscopic removal from the anorectum (Haloob 1986; Osborne & Bennett 1978) have been described.

It is thought that uterine perforation occurs soon after insertion. Copper (present in all three devices in our series) causes considerable inflammatory response and omental adhesions (Key & Kreutner 1980; Bromham *et al.* 1981; Osborne & Bennett 1978). Erosion into the wall of bowel lying in the pelvis may take place. Sepsis may cause visceral erosion and is associated with local abscess formation. Osborne & Bennett (1978) commented on the dangerous situation where the threads are visible yet the device has penetrated the myometrium and is embedded in adjacent bowel; traction on the threads could then cause bowel trauma.

These cases draw attention to the importance of the correct management of the patient with invisible IUCD threads (Guillebaud 1980). Ultrasound scan should be performed to show whether part, or all, of a device lies within the uterine cavity. If an intrauterine position is confirmed, Spencer Wells' forceps, a thread retriever, hook or suction may be employed to remove it. If the IUCD is not seen within the uterus, plain abdominal radiographs in two planes should define the position. Films of the whole abdomen may be necessary. A uterine marker (such as a second intrauterine device) is desirable. If the device is thought to be intraperitoneal, laparoscopy should precede laparotomy.

The presence of sepsis demands urgent localization and removal of the IUCD. Appropriate antibiotic therapy should be instituted; bowel repair, resection or colostomy may be necessary.

The possibility of IUCD perforation in the pregnant woman should be remembered. First trimester examination is mandatory and if the threads are not located it should not be assumed that the device has been expelled. Similarly, the placenta and membranes must be carefully examined at delivery. Unnoticed expulsion is relatively rare, and translocation of the IUCD must be actively excluded.

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References

Abdalla, O. (1984) Perforation of the rectum by a Lippes loop. *Br J Fam Plann* **9,** 117-118

Anonymous (1982) *Drug Ther Bull* **20,** no. 18, 69-72

Bromham, D R (1981) Difficulties with IUD removals. *Update* **22,** 961-973.

Bromham, D., Firth, G M & Fothergill, D J (1984) Sigmoidoscopic recovery of a displaced IUD *Br J Fam Plann* **9,** 125-127

Goldman, G A., Peleg, D., Feldberg, D , Dicker, D & Samuel, N (1983) IUD appendicitis Case report. *Eur J Obstet Gynaecol Reprod Biol* **15,** 181-183.

Guillebaud, J (1980) Scheme for management of lost IUD threads *IPPF Med Bull* **14,** 1-3

Haloob, R (1986) Lost intrauterine contraceptive device removed by proctoscopy *Br J Fam Plann* **12,** 65-66

Heartwell, S. F. & Schlesselman, S (1983) Risk of uterine perforation among users of intrauterine devices *Obstet Gynecol* **61,** 31-36.

Ismail, R. A. (1977) Translocated IUDs and missing strings. *S Afr Med J* **52,** 233-236.

Key, T C. & Kreutner, A. K. (1980) Gastrointestinal complications of modern intrauterine devices *Obstet Gynecol* **55,** 239-244.

Osborne, J L. & Bennett, M J (1978) Removal of intra-abdominal intrauterine contraceptive devices *Br J Obstet Gynaecol* **85,** 868-871.

Siddle, N. (1984) Risks of intrauterine contraceptive devices *Br Med J* **288,** 1554-1555.

Smith, P. A , Ellis, C. J , Sparks, R. A. & Guillebaud, J (1983) Deaths associated with intrauterine contraceptive devices in the United Kingdom between 1973 and 1983 *Br Med J* **287,** 1537-1538.

Tietze, C & Lewit, S (1970) Evaluation of intrauterine devices: ninth progress report of the co-operative statistical program *Stud Fam Plann* **55,** 1-40.

Tushuizen, P. B. & Ubachs, J M (1973) Perforation of the large bowel by a Lippes loop. *J Obstet Gynaecol Br Commonw* **80,** 854-855

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Ureteric band obstruction of the small bowel following radical hysterectomy. Case report

D. B. HOCKEN, P. D. KAPFF

Case report

A 44-year-old woman was admitted with a 36-h history of colicky central abdominal pain and nausea. Four years before she had been treated with radiotherapy and Wertheim's hysterectomy for Stage IIa carcinoma of the cervix. On examination she was pyrexial, the abdomen was distended and there was lower abdominal peritonitis with increased bowel sounds. At laparotomy there was an ischaemic loop of small bowel obstructed by a band crossing the pelvis. In order to deliver the bowel the band was divided and found to be the right ureter. A small bowel resection and anastomosis with primary ureteric repair over a pigtail stent were performed. Postoperatively the patient developed a pelvic abscess requiring an ileostomy, mucous fistula and cutaneous ureterostomy at a second operation with a good recovery.

Discussion

This is the first known report of intestinal obstruction due to an undivided ureter. Hay (1981) has reported obstruction due to a re-implanted ureter. It is perhaps surprising that this complication has not previously been reported when one considers how the mobilized ureter hangs across the pelvis (Kickham 1961). This case suggests that ureteric hitch procedures will prevent this complication as well as other ureteric complications following radical gynaecological surgery (Green 1966). Surgeons should be aware of this possibility when operating on patients with intestinal obstruction who have previously undergone Wertheim's hysterectomy.

Finally, we would wish to emphasize that both ends of an obstructing band should, if possible, be identified before division, though in this case division was essential to enable the bowel to be delivered.

References

Green, T. H. Jr (1966) Ureteral suspension for prevention of ureteral complications following radical Wertheim hysterectomy *Obstet Gynecol* **28,** 1-11

Hay, D. J (1981) Acute small bowel obstruction 20 years after reimplantation of the ureter. *Br J Urol* **53,** 83

Kickham, C J. E (1961) Urologic problems in carcinoma of the cervix *Surg Gynecol Obstet* **112,** 27-32

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Department of General Surgery and Urology, Royal Devon and Exeter Hospital
D. B HOCKEN
P. D KAPFF

Correspondence Mr D. B Hocken, FRCS, Research Fellow, Department of Surgery, Charing Cross Hospital, Fulham Palace Road, London W6 8RF

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BLAIR BELL RESEARCH SOCIETY

Papers presented at the meeting in September 1987 at Oxford

Doppler flow velocity waveforms in pregnancy-induced hypertension by K. P. Hanretty, M. J. Whittle & P. C. Rubin. University Departments of Midwifery and Materia Medica, The Queen Mother's Hospital, Glasgow

Although abnormal fetal and maternal Doppler flow velocity waveforms (FVW) have been described in association with pre-eclampsia, the mechanisms whereby these abnormalities may be produced is unclear. To determine the role of hypertension alone we have measured the pulsatility index (PI) in the umbilical and arcuate arteries in patients with non-proteinuric pregnancy-induced hypertension (PIH). Using a continuous wave Doppler unit, we have studied 45 patients with PIH. Comparisons were made with 35 normal pregnancies using the Mann–Whitney test. The mean umbilical artery PI in the PIH group was 0·6 (SE 0·04) which was similar to that in the normal group, mean 0·6 (SE 0·04). The mean arcuate artery PI was 0·91 (SE 0·04) in the PIH groups and 0·85 (SE 0·02) in the normal group. Eight patients were treated with 50 or 100 mg atenolol (Stuart Pharmaceuticals Ltd, Cheadle, Cheshire) and compared with eight patients with PIH who were treated with bed-rest alone. A further eight normal patients were also studied. Between 5 and 9 days after treatment began, the PI was measured in arcuate and umbilical arteries and the three groups were compared using non-parametric analysis of variance. Maternal and fetal heart rates were lower in the atenolol group ($P<0{\cdot}01$). There were no differences in any Doppler indices between the three groups. All the women had normal blood flow velocity waveforms before treatment. We conclude that in patients with PIH neither hypertension nor beta blockade affect blood velocity waveforms in the fetoplacental and uteroplacental circulations.

Treatment of polycystic ovary syndrome (PCO) with pure follicle-stimulating hormone (FSH) or human menopausal gonadotrophins (hMG) by P. B. McFaul*, A. I. Traub*, B. Sheridan† & H. Leslie†. *Department of Midwifery and Gynaecology, Queens University, Belfast, and †Endocrine Laboratory, Royal Victoria Hospital, Belfast

Seventeen patients with PCO who had failed to ovulate with clomiphere citrate had 52 cycles treated with intramuscular FSH (Metrodin, Serono, Herts) two ampoules daily, or four ampoules on alternate days, or pulsatile subcutaneous FSH starting at 6 i.u. every 90 min, or intramuscular hMG (Pergonal, Serono, Herts) two ampoules daily. Premature luteinization occurred in 3/11 (27%), 5/12 (42%), 12/16 (75%) and 5/13 (38%) of cycles respectively. Hyperstimulation was more common in cycles treated with Pergonal (42%) than in cycles treated with Metrodin (11%). The overall 'apparent' ovulation rate as determined by mid-luteal serum progesterone was 94%, and in cycles with premature luteinization was 96%. Six pregnancies resulted from treatment, three associated with premature luteinization ended in miscarriage, the other three have reached 28 weeks gestation. These data confirm that premature luteinization occurs in patients with PCO having gonadotrophin therapy independent of the mode of treatment, and that Pergonal results in more hyperstimulation than Metrodin. The assessment of ovulation by a single mid-luteal serum progesterone is inadequate and may account for the discrepancy between ovulation and pregnancy rates in these patients.

Umbilical artery velocity waveform assessed as an antenatal screening tool for intrauterine growth retardation and poor fetal outcome by R. B. Beattie, J. C. Dornan, C. W. A. Clements & B. McGrath. Royal Maternity Hospital, Belfast

The use of Doppler umbilical artery waveform studies for antenatal screening of intrauterine growth retardation (IUGR) and fetal compromise was assessed in a double-blind study. Waveforms were obtained from 2097 patients attending the antenatal clinic. Recordings were obtained at 28, 34 and 38 weeks gestation by 4 MHz continuous waveform Doppler ultrasound using a Doptek 9000 Spectrum Analyser (Doptek Ltd, Chichester, UK). The diagnosis of fetal compromise was made retrospectively by the clinicians and independently of the authors. Low birthweight-for-gestation (≤5th centile), skinfold thickness, Ponderal index and mid-arm circumference measurements were used to identify IUGR. The 5-min Apgar score, cord packed cell volume and umbilical artery acid base status were used to identify the hypoxic fetus. We found that the distribution of all three waveform indices, pulsatility index (PI), the A/B ratio and resistance index (RI) showed a marked right-sided (positive) skew not corrected by log transformation, and the PI at 28 weeks had a bimodal distribution. Values >90th centile defined an abnormal index. There was a statistically significant association between IUGR (<5th centile birthweight/gestational age) and an abnormal index with a sensitivity of 20–31%, specificity of 85–94% and a positive predictive value of 10–15%. The sensitivity was only increased to 43% when any abnormality of the PI, A/B ratio or RI was defined as an abnormal result. There was poor correlation between the Doppler indices and the other measures of fetal outcome described. All the unexplained stillbirths in the series had had an abnormal placental RI antenatally but had shown no clinical grounds for concern. We would therefore conclude that antenatal Doppler ultrasound used as a three-stage test is not a useful screening tool for the prediction of IUGR, perinatal asphyxia, polycythaemia, or fetal distress but there may be fetoplacental circulatory changes predating death in some unexplained stillbirths.

Power spectral analysis of the fetal heart rate during labour by M. J. R. Parker, J. C. Dornan, B. S. Sharif, R. H. Mitchell & J. G. Jenkins. Department of Midwifery and Gynaecology, Queens University, Belfast

Current attempts to quantify fetal heart rate (FHR) variability as a measure of fetal well-being in labour have proved unsatisfactory. Power spectral analysis is a new and previously untried technique for the objective quantification of FHR and determines the frequency of its oscillations. Using a dedicated microprocessor system a sample of 512 R-R intervals is derived from the fetal ECG. This time-based sample is then subjected to Fast Fourier Transform which converts the signal to a frequency-based signal before spectral analysis. We have established a normal range during labour for 200 patients in spontaneous labour with a normal obstetric history. The frequency distribution of spectral power exhibits a positive skew but when log transformation was applied the transformed values approximated to a normal distribution and data analysis was determined using these log transformed values. The range was described using mean and 95% confidence intervals for low and high spectral power during early labour, at 5 cm dilatation and second stage. The ranges for low spectral power (0·005–0·02 Hz) were 3289 (2624–4129), 3524 (2773–4477) and 4276 (3170–5768) at each time sampled. The ranges for high spectral power (0·1–0·2 Hz) were 2466 (2070–2938), 2312 (1950–2742) and 2972 (2360–3741). In newborn infants spectral power has been shown to correlate well with outcome, therefore, having determined a normal range in the fetus during labour, we are now investigating the value of power spectral analysis of the FHR as a determinant of fetal compromise.

Should vaginal examination be recommended to all women in the antenatal booking clinic for reasons other than cervical smear? by P. O'Donovan & R. J. Lilford. Departments of Obstetrics and Gynaecology, The General Infirmary and St James's University Hospital, Leeds

The benefits of routine vaginal examination at booking of pregnant women were examined by retrospective review of 11 622 consecutive case records. Sixteen ovarian cysts including one of borderline malignancy and 10 trichomonal vaginal discharges were detected. There were no cases of cervical incompetence or ectopic pregnancy suspected on the basis of vaginal examination. If a recent smear has been negative and routine ultrasound is planned anyway for dating and diagnosis for multiple pregnancy the major remaining benefit would be the early detection of ovarian malignancy. We estimate that at least 300 000 vaginal examinations would be required to prevent one maternal death from this cause. A survey of attitudes in 200 women showed that 55% considered vaginal examination unpleasant and 20% even thought that it might cause miscarriage. A survey of 30 doctors indicated that 80% would only consider vaginal examination worthwhile if the chance of diagnosing a lethal curable condition was greater than 1 in 100 000. We therefore conclude that in our population routine booking vaginal examination is not justified if a recent smear is negative and ultrasound examination is planned

Screening of the high-risk renal transplant recipient. Immunological changes in the cervix by R. J. S. Hawthorn*, D. Tillman†, M. Watson‡, J. D. Briggs‡ & A. B. MacLean*. *Department of Gynaecology, †Department of Dermatology and ‡Department of Renal Medicine, Western Infirmary, Glasgow

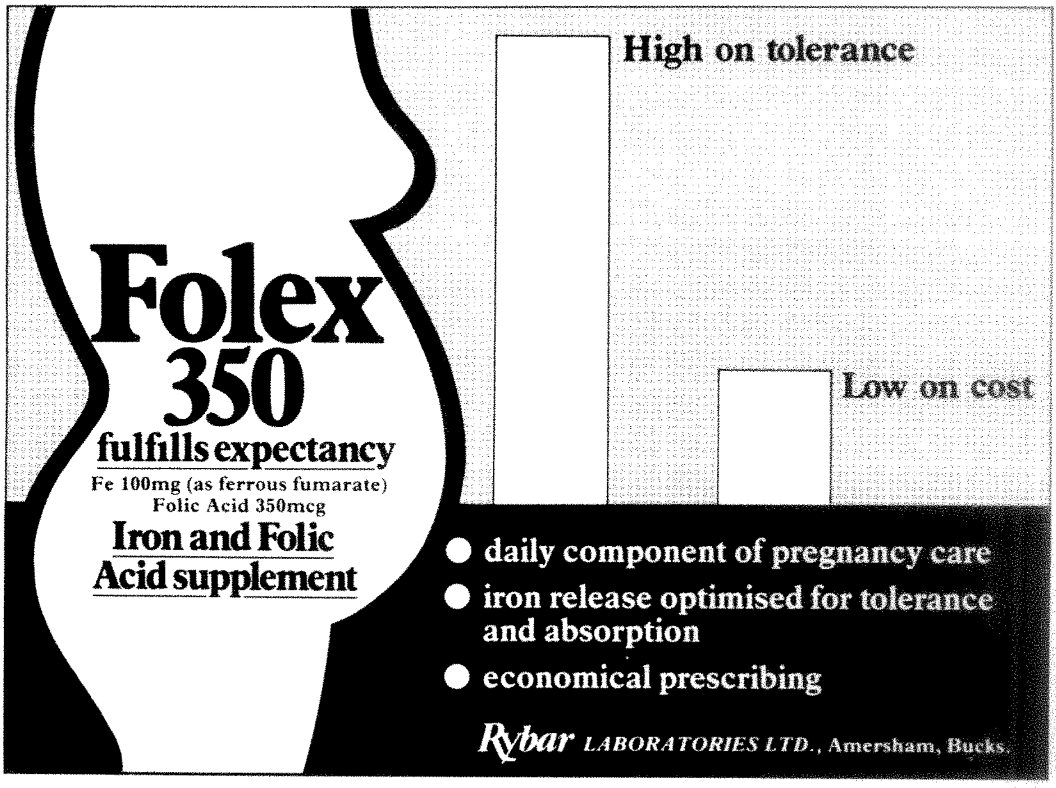
As women on immunosuppressant therapy after a kidney transplant are known to be at high risk of pre-invasive and invasive lesions of the lower genital tract, we began routine colposcopic and cytological screening. Punch biopsies of cervix were also taken to determine changes occurring locally in the immunocompetent cells in the cervix which might predispose to viral infection and neoplastic change. Thirty-eight patients have been examined in a combined approach involving the colposcopist and dermatologist. Three patients had abnormal cervical cytology, but six patients had evidence of cervical intraepithelial neoplasia on colposcopically directed punch biopsy. Twelve patients had histological evidence of virus infection, all had cutaneous warts. Immunohistochemical studies *in situ* showed a significantly reduced population of epithelial Langerhan's cells, and helper T-cells were also significantly reduced when compared with normal values. Impaired local cellular immunity may be one reason why this group of patients has a high prevalence of wart virus infection and cervical precancer, but cervical cytology alone does not appear to be an adequate screening test in these patients.

A survey of the values which women attach to caesarean section and vaginal delivery by J. G. Thornton & R. J. Lilford. Departments of Obstetrics and Gynaecology, The General Infirmary and St James's University Hospital, Leeds

We interviewed 81 unselected non-pregnant women, 14 women who had requested home confinement and 18 pregnant women by a lottery technique to find the fetal risks at which they would wish to undergo caesarean section for fetal benefit. Each woman was told to assume no net maternal risk from operation, a background perinatal mortality of 10 per 1000 and informed that caesarean delivery could be under general or local anaesthesia and would need repeating in future pregnancies. By asking her to choose the mode of delivery at various fetal risks of death preventable by caesarean section a level of indifference was determined. The unselected non-pregnant women were indifferent at a median fetal risk of 1 in 4000, the home-delivery women at a risk of 1 in 100, and the pregnant women at 1 in 20 000. These results appear plausible and suggest that, apart from the home delivery group, the women were very fetal risk averse. However, the underlying attitudes of 36 of the women were also tested by measuring the degree to which two groups of emotionally significant words interfered with a colour naming task. The groups included either bad fetal outcome words such as 'stillbirth' and 'dead baby' or medical intervention words such as 'caesarean section' and 'forceps'. The colour naming delays elicited did not correlate with the lottery and indicated that the lottery results should be interpreted with caution.

Gonococcal and chlamydial antibodies in ectopic and intrauterine pregnancies by J. N. Robertson, P. Hogston* & M. E. Ward. University Department of Microbiology, Southampton General Hospital, and *Department of Obstetrics and Gynaecology, Princess Anne Hospital, Southampton

Sera from 50 women with ectopic pregnancy and 50 age-matched control women with intrauterine pregnancy were tested by enzyme-linked immunosorbent assay (ELISA) using *Chlamydia trachomatis* and *Neisseria gonorrhoea* pili as antigens. In the ectopic pregnancy group, 76% had IgG antibodies to *C. trachomatis* compared with 38% in the control group ($P<0{\cdot}0001$). The prevalence of gonococcal IgG antibody was 32% in the ectopic pregnancy group and 4% in the control group ($P<0{\cdot}001$). The absence of IgA antibodies to the two organisms suggested that the infections were not recent, and this was corroborated by our failure to grow *C. trachomatis* from any cervical swab from the ectopic pregnancy group. Chlamydial antigen was detected (by ELISA) in exfoliated cervical cells of only one patient in this group.



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Forthcoming RCOG meetings in 1988

15-16 September	Joint meeting with District VII of the American College of Obstetrics and Gynecology on "Endometriosis and New Advances in Gynecological Imaging"
7-8 October	Diplomates' course for General Practitioners
20 October	Postgraduate meeting on "Benign Gynaecological Conditions"
9 November	Scientific meeting on "AIDS in Obstetrics and Gynaecology"
28 November- 2 December	Consultants' Conference

Further details are available from:- **Miss B J Stevens, Postgraduate Education Department, Royal College of Obstetricians and Gynaecologists.**

THE CASE
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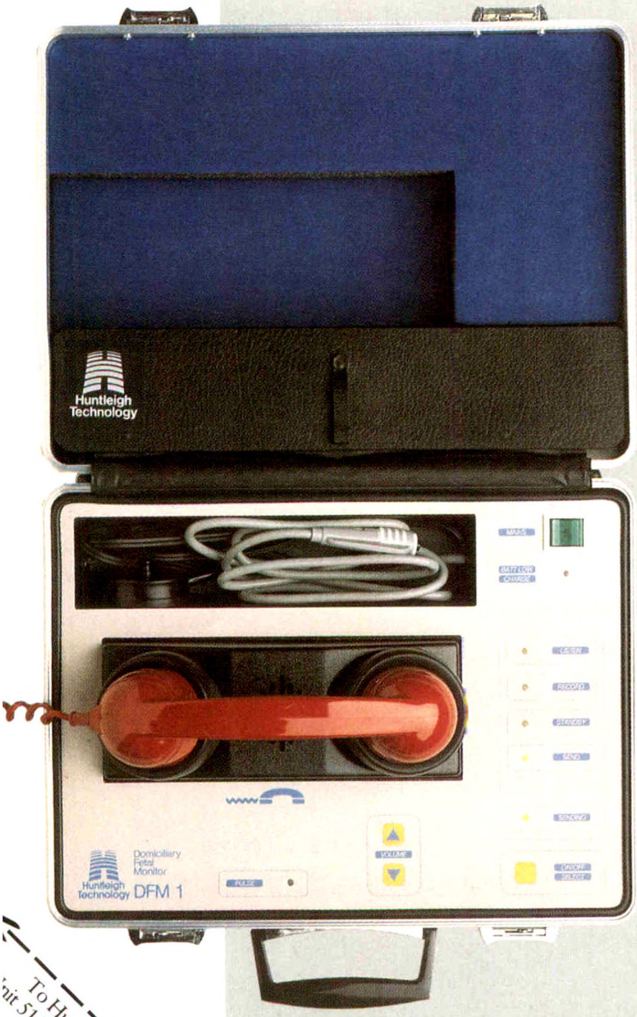
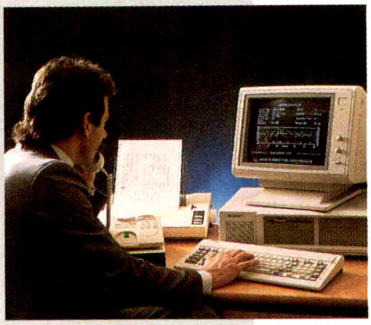
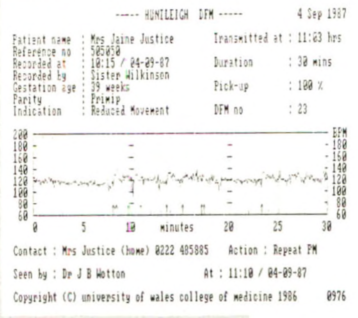
BY TELEPHONE





Huntleigh DFM allows antepartum monitoring to be carried out at the patients home or healthcentre...



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----- HUNILEIGH  DFM -----                4 Sep 1987

Patient name   : Mrs Jaine Justice     Transmitted at : 11:03 hrs
Reference no   : 505050
Recorded at    : 10:15 / 04-09-87      Duration       : 30 mins
Recorded by    : Sister Wilkinson
Gestation age  : 39 weeks              Pick-up        : 100 %
Parity         : Primip
Indication     : Reduced Movement      DFM no         : 23
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200
180
160
140
120
100
80
60
BPM
0
5
10
minutes
20
25
30

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Contact : Mrs Justice (home) 0222 485885   Action : Repeat PM

Seen by : Dr J B Wotton                 At : 11:10 / 04-09-87

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British Journal of Obstetrics and Gynaecology
May 1988, Vol. 95, pp. 537–539

CORRESPONDENCE

Commentary: The safety of diagnostic ultrasound

Dear Sir,

It is surprising that, when in his timely commentary on the safety of ultrasound [*Br J Obstet Gynaecol* (1987) **94**, 1121–1122] Dr Meire referred to the lack of arrangements for training medical users of ultrasound apparatus, he made no mention of the recent Report of the Joint Ultrasound Group of the Royal College of Obstetricians and Gynaecologists and the Royal College of Radiologists (1987). As a fellow of the latter college, he must have received a copy of the report, just as did every UK-based member and fellow of the Royal College of Obstetricians and Gynaecologists.

As summarized in its report, the aim of the Joint Ultrasound Group was 'to establish an approved training syllabus for obstetricians and radiologists, so that in the future every consultant obstetric unit will have at least one expert in obstetric ultrasound to organise, represent and supervise the service, to scan problem cases on a regular basis, to understand the significance of abnormal findings and to recommend appropriate management'. These duties and skills represent second level obstetric ultrasound.

While the group did not deal with the attainment of first level proficiency, it declared its support for 'the view that ultrasound should be regarded as an extension of the hands, eyes and ears of the obstetrician, and therefore that in future every trained obstetrician should be able to carry out simple scanning (e.g. to confirm fetal life, to identify fetal number and presentation, to obtain a fetal measurement for the assessment of gestational age, and to locate the placenta)'. Achievement of these basic skills must now be recognized to be an essential part of practical obstetric training and of MRCOG requirements; and the Royal College of Radiologists requires its fellowship candidates to have had the practical experience of at least 75 h of supervised obstetric ultrasound scanning.

The Joint Ultrasound Group did not seek to contribute to 'multiple diplomatosis' through establishment of an examination and certification process, just as for example the British Society for Colposcopy and Cervical Pathology, while setting standards and running training courses, has not advocated additional examining and certifying procedures for gynaecologists and pathologists working in its special field.

The two royal colleges have, as recommended by their Joint Ultrasound Group, established a standing joint committee to promote standards in obstetric ultrasound, and to regulate and monitor the proposed training arrangements. It is hoped that all obstetricians and radiologists active in this important field will welcome and support this development, and that those in a position to do so will establish the necessary training centres, programmes and courses.

C. R. Whitfield
Professor
University Department of Midwifery
The Queen Mother's Hospital
Glasgow G3 8SH

References

Meire, H. B. (1987) Commentary: The safety of diagnostic ultrasound. *Br J Obstet Gynaecol* **94**, 1121-1122.

Royal College of Obstetricians and Gynaecologists and Royal College of Radiologists (1987) *Report of the Joint Ultrasound Group of the RCOG and RCR.* RCOG, London.

Authors' reply

Dear Sir,

I am of course aware of the report of the Joint Ultrasound Group and of its detailed contents. There is little in Professor Whitfield's letter with which I can take issue; in general I share his views completely. The only area in which our views may differ somewhat is over the question of certification of competence. As he says, ultrasound is essentially a practical technique and if trainees have merely attended a relevant course it certainly cannot be assumed that they are competent to perform the technique. My personal view is that some form of examination and certification would be advisable if minimum standards were to be guaranteed. This does not necessarily have to involve the granting of a diploma and could certainly be incorporated into the membership and fellowship exams of the two colleges.

Despite the recommendations of the joint colleges there is currently no mechanism for guaranteeing that trainees have fulfilled the minimum requirements for practical ultrasound experience and they will certainly not be examined in their ability to perform this essentially practical procedure.

I know that both the colleges and Professor Whitfield and myself all have the best interests of our patients in mind, my intentionally controversial commentary was written with the express intent of stimulating discussion of the subject in the hope that this will make some contribution towards furthering the goal of improving the performance of diagnostic ultrasound investigations.

H. B. Meire
Consultant Radiologist
King's College Hospital
Denmark Hill
London SE5

Reproductive performance following conservative microsurgical management of tubal pregnancy

Dear Sir,
Since a number of consultants in this country still forbid their juniors to conserve fallopian tubes when treating tubal pregnancies, the paper by Oelsner *et al.* [*Br J Obstet Gynaecol* (1987) **94**, 1078–1083] was timely indeed. I would like to make three points about the paper.

(1) The authors expressed their results in terms of the intrauterine pregnancy rate and the proportion of pregnancies which were ectopic, and admonished others to do likewise. But, since no one is interested in miscarriages, the live birth rate is much more relevant. How many of the 26 patients who had an intrauterine pregnancy had one or more live births subsequently? Further, as the authors point out, conception rates are a function of time, so 'rates' should be calculated by actuarial methods either parametric or non-parametric. The appropriate non-parametric test to compare pregnancy rates at 1 year, for example, is the log-rank test, and not the Mann–Whitney test, which the authors used. Did the intrauterine pregnancy rates at 1 year differ between women who had a single tube and those who had both tubes present?

(2) The authors did not suggest which conservative procedure should be regarded as the operation of choice. In this country, where almost all ectopic pregnancies are treated by junior doctors unsupervised by consultant staff, it must surely be linear salpingostomy without closure of the incision as this is a simple operation requiring no special training or equipment. As the authors state, there is no evidence that any other operation produces any better results, and this is even true of pregnancies which are in the isthmus (Smith *et al.* 1987), contrary to what some 'reproductive surgeons' have suggested on very meager evidence (Maheaux & DeCherney 1985). On the other hand, there is some evidence to suggest that 'milking' the pregnancy out of the tube is associated with a higher rate of recurrent ectopic pregnancy than is found after salpingostomy and although the difference falls short of statistical significance due to small numbers, most previous data have shown this trend. The pooled ectopic pregnancy rates (including the authors' data) after 'milking' and salpingostomy are 23% and 17%, respectively, and the ectopic/intrauterine pregnancy ratios are 68% and 38%, respectively (Caspi & Sherman 1987). It is perhaps notable that all favourable reports pertaining to this operation have emanated from Israel. One should, therefore, at least think twice before resorting to this procedure, and be certain that the pregnancy is fimbrial and almost completely aborted already.

(3) The authors hinted (p. 1081) that they believe the recurrent ectopic pregnancy rate to be in fact higher (but acceptably so) after a conservative procedure, and I believe they are probably correct in their view. Many factors other than the operation influence the pregnancy rates, such as age, parity, state of the contralateral tube and pelvis, length of follow-up. Since these factors were not taken into account when the conservative and ablative procedures were compared, virtually no conclusions can be drawn from such comparisons other than that the rates are not wildly different. The most potent argument against this view is the finding that recurrent ectopic pregnancies after a conservative procedure are located in the contralateral tube as often as in the conserved tube

(Hallett 1986). However, this does not mean that the conserved and the contralateral tubes are associated with identical ectopic/intrauterine pregnancy ratios. Indeed, the only study in which patients were matched for age and parity showed not only a higher recurrent ectopic pregnancy rate after salpingostomy (9 of 48) than after salpingectomy (6 of 50), but almost double the ectopic/intrauterine pregnancy ratio after conservative surgery (47% compared with 28%), even though 5 of the 9 recurrent ectopic pregnancies after salpingostomy were in the contralateral tube (DeCherney & Kase 1979).

Clearly, there is much to be learned, but the available information does not justify *carte blanche* conservatism. For example, I doubt if it is wise to conserve a tube which has been previously operated upon, either because of a previous ectopic pregnancy or because of occlusion. I wonder if the authors' data can shed light on this point.

Nicholas Kadar
Director of Gynecologic Oncology
Department of OB-GYN
Hahnemann University
Philadelphia
PA 19102–1192
USA

References

Caspi, E. & Sherman, D. (1987) Tubal abortion and infundibular ectopic pregnancy *Clin Obstet Gynecol* **30,** 155-163.

DeCherney, A. H. & Kase N. (1979) The conservative surgical management of unruptured ectopic pregnancy. *Obstet Gynecol* **54,** 451-455

Hallatt, J G. (1986) Tubal conservation in ectopic pregnancy: a study of 200 cases *Am J Obstet Gynecol* **154,** 1216-1221

Maheaux, R & DeCherney, A H (1985) Surgical management of tubal pregnancy *Semin Reprod Endocrinol* **2,** 175-181

Smith, H. O , Toledo, A. A & Thompson, J D. (1987) Conservative surgical management of isthmic ectopic pregnancies. *Am J Obstet Gynecol* **157,** 604-610.

Authors' reply

Dear Sir,
Concerning the live birth rate, our paper refers to the number of pregnancies, as the point of the paper is to demonstrate tubal function after tubal surgery. Of the 26 intrauterine pregnancies, five (19%) ended in miscarriage.

We take Mr Kadar's point about conservative procedures being performed by inexperienced junior staff. We agree that salpingostomy requires less dexterity and experience than salpingotomy. However, if the tube is closed with 6/0 nylon it is possible to dispense with the microscope if the principles of microsurgery are observed (gentle tissue handling, continuous irrigation, etc). In addition, the results of salpingotomy are equal to those of salpingostomy.

As for isthmic pregnancies, there are very few results available. This may be due to isthmic pregnancies being rare. When they present, a high proportion have ruptured. This situation requires resection with end-to-end anastomosis.

We agree with Mr Kadar that milking should be reserved for pregnancies aborted into the tubal lumen. The role of milking is merely to expel the pregnancy, not to detach it. The high recurrent ectopic pregnancy rate after milking may be due to vigorous milking to remove a firmly attached pregnancy. The trauma caused by such a vigorous procedure could cause more damage than good and hence predispose to a subsequent ectopic pregnancy.

We did not match for age or parity but these variables are not in themselves causative factors in the pathogenesis of ectopic pregnancy. Even when the contralateral tube appears normal at operation its endosalpinx could still be pathological. As Mr Kadar notes, Hallatt (1986) found that after a conservative procedure, both tubes were at equal risk of recurrent ectopic pregnancy. We do therefore think that our figures are significant.

We do not perform a conservative operation on a tube previously operated upon, whether for previous ectopic pregnancy or tuboplasty.

G. Oelsner
H. Karp
Department of Obstetrics and Gynecology
Chaim Sheba Medical Center
Tel Hashomer 52621
Israel

British Journal of Obstetrics and Gynaecology
May 1988, Vol. 95, pp. 540–544

BOOK REVIEWS

An Introduction to Fetal Physiology by Frederick C. Battaglia & Giaccomo Meschia. Academic Press, Inc., London, 1986, 256 pages with figures and tables, £37.50

This book is a continuation of the Donald Barron school of fetal physiology. Both the authors of this volume learned from the master and continued their thoughts and work in a way of which Dr Barron would have approved. They now work at Denver, in the Paediatric and Perinatal Departments and their book reflects enormously the influence of Barron on fetal physiology in America.

Battaglia and Meschia quite rightly point out that much of the data produced by fetal physiologists working with different species are conflicting. They endeavour to show us those data that support the establishment of the principles of fetal physiology and succeed in upholding the broader implications of the subject. The authors use the differences between species to emphasize that mammalian reproduction covers a whole spectrum of behaviour but that the physiology fits into certain basic principles that can apply, whatever species is being examined.

Naturally, fetal growth takes first place in this book for this is one of the earlier areas of measurement ending with the use of ultrasound to allow us to use longitudinal studies rather than cross-sectional data in several experimental instances. In some centres, animal fetal physiologists have been slow to take up ultrasound as a measure but its use provides another weapon in the armamentorium of measurement. An excellent review of placental transfer follows and there are chapters on metabolism which review carefully the measurement methods, pointing out their difficulties.

Fetal respiratory and cardiovascular physiology follow, giving critical reviews of the studies which are often accepted as gospel, but have problems of interspecies interpretation.

Uteroplacental blood flow is considered in the eighth chapter, but one misses any critical account of Doppler ultrasound measurement which is mostly used in human uteroplacental blood flow measurements. The final chapter is on fetal water balance, probably an area of fetal physiology often neglected, yet most important. An excellent account occurs in this chapter.

This book is essential for all who want to gain a real understanding of fetal physiology. It goes into the background, bringing Barcroft into the 1980s. It is a volume which should be held by all medical schools and all those who work in fetal physiology; if only for source references, it would be well worth its value. More than this, it is a well written and well thought out account of fetal physiology by men who have been in the subject for long enough to have seen it from its puberty to its maturity.

Geoffrey Chamberlain

Endometriosis edited by Emery A. Wilson. Alan R. Liss, Inc., New York, 1987, 233 pages with figures and tables, £24.00

The editor of this multi-author book uses a quote from Sir Winston Churchill to describe our present knowledge of endometriosis: ‘A riddle wrapped in a mystery inside an enigma’. Perhaps he was motivated to assemble this group and produce the book in an attempt to solve this riddle. This objective has not been attained, through no great fault of the authors, as the aetiology of the condition and its relation to infertility remains unsolved. Perhaps he was also motivated to help improve the standard of care of patients with endometriosis. Certainly in the chapter on surgery and medical treatment there is a large amount of useful information which may lead some to change their current practice. There are some surgical approaches that are not widely carried out in this country, notably the operation of presacral neurectomy for the treatment of central pelvic pain associated with endometriosis in the woman who wishes to preserve her fertility. It is also more usual to remove an uninvolved ovary when operating on a patient who no longer desires fertility, as most authorities in this country would be concerned not only about the development of endometriosis within that ovary, but also about the stimulation of any endometriotic deposits that have not been eradicated by conservative surgery. Most gynaecologists would expect some reference to adenomyosis in a book on endometriosis, but the editor emphasizes that it is pathologically and clinically an entirely separate entity with different aetiological presentation and treatment. In spite of this, I found the omission surprising and a chapter could easily have been added without any detrimental effects.

This is not a book to read from cover to cover, as there is the inevitable repetition which occurs when a number of authors are involved. I do not see it adorning the bookshelves of any but the practitioner with a particular interest in endometriosis. However, there is a large amount of useful information in this book, together with an excellent bibliography. It is a valuable reference book which should be in gynaecological libraries.

A. T. Letchworth

Quantitative Obstetrical Ultrasonography edited by Russell L. Deter, Ronald B. Harrist, Jason C. Birnholz & Frank P. Hadlock. John Wiley & Sons, New York, Chichester, 1986, 377 pages with figures and tables, £43.25

The authors have written a valuable and unusual book covering the methodology used and results obtained in the relatively new field of obstetrical ultrasonography. The published literature is already extensive, so this book is designed to meet the following needs of clinicians: (1) to have adequate access to the information available; (2) to understand how the data were collected; (3) to determine whether a given subject has been studied appropriately; (4) to identify reliable information for use in specific clinical situations; and (5) to follow new developments. To meet these needs the book is divided into five sections covering basic concepts, dating, growth, dynamic processes, and statistical methods. The main text covers 277 pages of which about 100 are devoted to statistics. There are also 87 pages of appendices giving structured summaries of the published studies on fetal dating, normal growth, growth curve models, fetal weight estimation, and the detection of fetal growth abnormalities.

The book opens with a short review of ultrasound technology. Next comes an important chapter describing the ideas behind the authors' evaluation of obstetrical ultrasound studies. The following six chapters give comprehensive reviews of the literature, in conjunction with the standardized evaluations of each paper in the appendices. The last section of the book gives a somewhat concentrated introduction to statistical concepts and methods of analysis. It would probably be difficult to learn statistics from scratch using these chapters, but the information is more reliable than that found in many introductory statistics textbooks. These chapters would be very useful for someone with prior exposure to statistics, giving revision of basic methods and introducing some methods, such as multiple regression, that are of specific relevance to fetal measurement. There are sensible comments on many topics, such as randomization and the assumptions underlying hypothesis tests, but no comment on other important issues, such as the use of one- or two-sided tests.

The authors have been very successful in meeting their aims, and anyone interested in the subject will find much of value. The dearth of longitudinal studies is clearly seen, surely a prerequisite of a proper evaluation of fetal *growth*. I hope that this book will stimulate research in this and other neglected areas. One important criticism is the failure to distinguish between intrauterine growth retardation (IUGR) and light-for-gestational-age (often called small-for-gestational-age (SGA)). On page 57 it is wrongly stated that IUGR and SGA 'are identical conceptually'. The authors have missed the opportunity to condemn the widespread definition of IUGR as birthweight below the fifth centile, and to clarify terminology generally. A small criticism is the use of *parameter* to mean a measurement or variable, especially confusing when, as here, the word parameter is also frequently used in its statistical sense.

The book is well indexed and the production is of a high standard. In summary, a valuable book for clinicians and a must for researchers in the field.

Douglas G. Altman

Labor and Delivery: Impact on Offspring by E. A. Friedman & R. K. Neff. PSG Publishing Company, Inc., 1987, 523 pages with figures and tables, £49 50

This book is a detailed report based on the 'national collaborative perinatal project' (NCPP) of the National Institute of Communicative Disorders and Stroke carried out in the United States of America between 1958 and 1974. In many ways this study was similar to the National Birthday Trust's 1958 study in the UK, but it collected more data about each patient, and the large numbers (almost 59 000 cases) were achieved by studying deliveries at 14 university hospitals over 6 years rather than studying all deliveries nationwide over a short period. A series of papers in the journals has long since reported the core results of the study and a previous book has detailed the data relating to pregnancy hypertension.

The current book reports in equal detail the results of the study relating to labour and outcome. Much attention is given to partographic analysis of the various protraction disorders and their association with mode of delivery and neonatal outcome. Other variables considered include drug usage and the standard obstetrical risk factors such as maternal age, weight, height and socioeconomic status.

The text is very detailed and this makes it difficult to read. There are many complex tables and the statistical analysis uses techniques such as cluster analysis, logistic regression analysis, and Freeman-Tukey deviate calculation. Much of the book is incomprehensible without at least a degree-level training in statistics. In addition Dr Friedman's style is not suited to easy comprehension. As he confesses in the preface, he frequently waxes both eloquent and prolix—unfortunately more often prolix than eloquent. A typical example is 'the adequacy of the maternal pelvis to accommodate to an average-sized fetus had been assessed clinically by careful digital examination in early pregnancy' (means 'pelvic assessment was performed at booking').

It is disappointing that 13 years after this valuable study ended, it has not been found possible to present the data in a more digested and accessible fashion. This book may have value for the select band of specialist obstetric epidemiologists but I suspect that most practising obstetricians will find it, as I did, largely incomprehensible.

Philip J. Steer

Fetal Physiological Measurements edited by Peter Rolfe. Butterworths, London, 1986, 342 pages with figures and tables, £50 00
Neonatal Physiological Measurements edited by Peter Rolfe. Butterworths, London, 1986, 476 pages with figures and tables, £45.00
(Both books cover Proceedings of the Second International Conference on Fetal and Neonatal Physiological Measurements, Oxford, 1984)

Conference reports are difficult to publish in an interesting way, and too often are out of date, fragmented and repetitive. Dr Rolfe has succeeded in avoiding most but not all of these pitfalls in this two-volume report of the Second International Conference on Fetal and Neonatal Physiological Measurements. A slim first volume covers papers and lectures on fetal measurements ranging from conventional heart rate analysis to intrauterine blood pressure and blood gas analysis, and the wide range of fetal ultrasound physiological measurements now possible

The second volume on neonatal measurements covers recent ideas in the field of respiratory mechanics, cerebral haemodynamics and blood gas analysis together with the latest developments in magnetic resonance and cerebral evoked potentials. The application of appropriate technology to developing countries is also given consideration in both volumes.

Although authors contributed manuscripts at the conference, the book has still taken 2 years to materialize. However, it is a tribute to the conference organizer that most of the material is still up to date. Professor Volpe's work on positron emission tomography curiously appears in much the same form in both volumes. It is difficult to know at whom these volumes are aimed, but research departments would find them a good guide to 'where we are at' in perinatal physiological measurement.

Richard Cooke

Atlas of Fetal Sectional Anatomy with Ultrasound and Magnetic Resonance Imaging G. Isaacson, M. C. Mintz & E. S. Crelin. Springer-Verlag, Heidelberg, 1986, 184 pages with figures and tables, DM228

The purpose of this book is to provide an anatomical atlas of the fetus to facilitate the interpretation of images obtained by ultrasound and magnetic resonance. Whole body sections are presented in the sagittal, coronal and transverse planes and a series of line diagrams are used to map the appearance of the sections in parallel with the ultrasound and magnetic resonance images.

The first thing that must be said is that the anatomical plates are superb and provide an excellent guide for any practitioner or technician involved in fetal imaging.

The second observation I would make is that the ultrasound images are generally made with the fetus *in utero*, whereas the magnetic resonance studies which use a powerful 1·5 tesla magnetic field are performed on the infant after delivery. This partly accounts for the superb quality of the magnetic resonance images. This type of field strength has not yet been used in human pregnancy *in vivo*. The only comparable images so far published of the fetal anatomy have been with resistive magnets with slow imaging times and, although these pictures have been excellent, they have been limited in definition because of fetal movement. It is likely, however, that images of the quality in this book which look very similar to the anatomical sections, will be produced in the future and will replace the use of ultrasound in some particular abnormalities. In the immediate future and irrespective of what happens in the imaging field, this is an excellent visual presentation of fetal anatomy. The book should be on the shelf of every ultrasonographer and will be invaluable to all teachers in obstetrics.

E. M. Symonds

Immunoregulation and Fetal Survival edited by T. J. Gill, III, T. G. Wegmann with E. Nisbet-Brown. Oxford University Press, Oxford, 1987, 324 pages with figures and tables, £40.00

This book originated from the second conference on 'Reproductive Immunology' held in Banff, Canada, in 1985. The first book in the series—*Immunology of Reproduction*—was published in 1983, emanating from the first Banff conference in 1981. Comparing the two was akin to looking at two sets of family photographs of one's children taken 5 years apart. Only then does one actually see how they have grown and developed in those years. In reproductive immunology, the two developments which have helped produce this dramatic change in such a relatively short time are the use of monoclonal antibodies and molecular genetic techniques. The change is in scope as much as in knowledge. The authors therefore were wise to focus this second volume on immunoregulation and genetic interactions at the materno–fetal interface.

The book begins with an integrative chapter by the editors on immunorecognition and genetic regulation. Discussions about maternal systemic immunity and the immunology of the decidua/endometrium and trophoblast follow. I personally found the second and third sections the most valuable of all. The remaining sections discuss immunological aspects of fetal survival, experimental models in mouse and equine pregnancy on recurrent miscarriage in women, and the whole ends with some thoughts about the future by looking at the past.

My only major criticism of the book is the same as that of the first in the series, namely that they were both published at least 2 years after the respective conferences. Fortunately the current pace of change has not been so great as to diminish the value of this book significantly. It is not, however, a book which is suitable for a young clinician with no background knowledge of immunology. That is not a criticism for it is not written with these in mind. The editors' stated objective is that it 'should be useful as a monograph for the investigator in reproductive immunology and as a text for the student contemplating specialisation in this field'. I believe it achieves that objective well by highlighting, summarizing and integrating the fascinating new information which has become available on immunoregulation over the past few years.

G. M. Stirrat

Neurological Disorders of Pregnancy edited by Phillip J. Goldstein. Futura Publishing, New York, 1986, 283 pages with figures and tables, $39.50

Neurological complications are uncommon in pregnancy and most obstetricians and neurologists have little experience of them. There is therefore a good case for putting together 'the combined body of knowledge'. This book has required 19 authors mainly from Johns Hopkins University, Baltimore, to do so.

In general I would recommend this text; all major topics are covered including excellent chapters on the American view of eclampsia (Sibbai), epilepsy (Krumholz), infections (Levin), cord injury (Cohen & Hilton), the peripheral nervous system (Cohen & Felsenthal), multiple sclerosis (McArthur & Young) and myasthenia (Repke & Klein).

My criticisms are relatively minor: there is no direct guidance on how to advise the woman with known cerebro-vascular disease in pregnancy (I believe that arteriovenous malformation is one of the few conditions where pregnancy is absolutely contraindicated). In the patient with prolactinoma and mild symptoms of tumour expansion there is undue emphasis on treatment with dexamethasone rather than bromocryptine demonstrating a traditional neurosurgical approach. Either the chapter on postpartum depression should be omitted since it is a psychiatric rather than a neurological disorder or it should be expanded to include a consideration of all the major psychiatric illnesses in pregnancy. Of course the author 'ducks out' of the problem of whether to use beta adrenergic blockade as prophylactic treatment in patients with migraine in pregnancy. The possible complications are listed and the reader is left to make up his own mind, a typical reaction from the USA where the fear of litigation is even greater than in the UK.

Despite these criticisms I would certainly recommend this book. It seems to be more related to pregnancy than the monograph by Donaldson on the same subject which appeared in 1978, but that book did have the the advantage of being written by a single author.

M. de Swiet

Books received some of which may be reviewed at a later date

Perinatal Practice Volume 5. Fetal and Neonatal Growth edited by Forrester Cockburn. John Wiley & Sons, Chichester, 1988, 216 pages with figures and tables, £37.50

Functional Disorders of the Menstrual Cycle edited by M. G. Brush & E. M. Goudsmit. John Wiley & Sons, Chichester, 1988, 303 pages with figures and tables, £45.00

The Health Scandal by Vernon Coleman. Sidgwick & Jackson, London, 1988, 245 pages, £12.95

Pelvic Surgery: A Multidisciplinary Approach edited by John H. Isaacs & Mitchel P. Byrne. Futura Publishing Company, New York, 1987, 229 pages with figures and tables, $32.50

Decision Making in Infertility edited by A H. DeCherney, M. L. Polan, R. D. Lee & S. P. Boyers. B. C. Decker, Inc., Toronto, Philadelphia, 1988, 215 pages illustrated, £33.45

Progress in Operative Gynaecology by S. K. Chaudhuri. B. I. Publications, New Delhi, 1987, 207 pages illustrated, $30.00 (subsidized price in India, Rs 85.00)

Actualités Gynécologiques 18ème Série edited by Pierre-Albert Netter & Andre Gorins. Masson, Paris, 1988, 356 pages with figures and tables, F295

Erratum

Book reviews

The Safety of Diagnostic Ultrasound (British Journal of Radiology Supplement 20) edited by P. N. T. Wells is published by the British Institute of Radiology and not the Royal Institute of Radiology as printed in *Br J Obstet Gynaecol* (1987) **94,** 1119.

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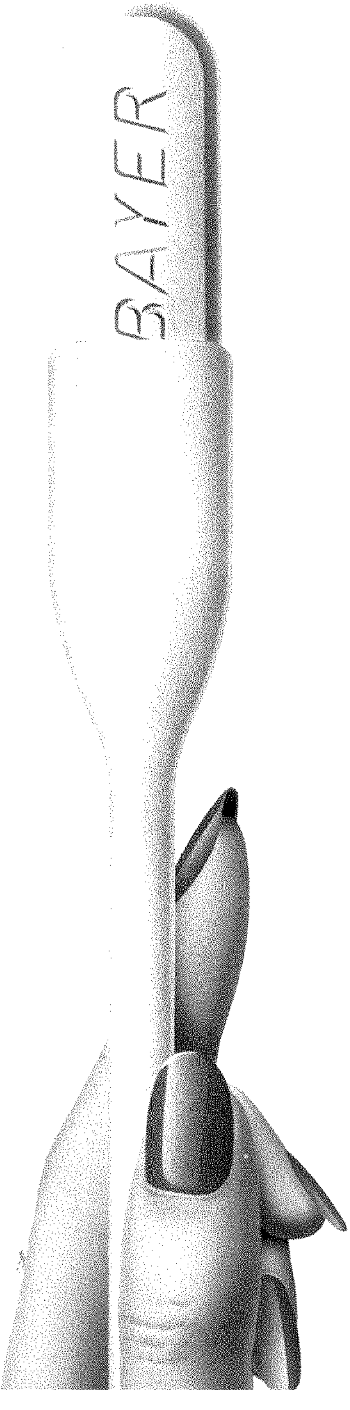

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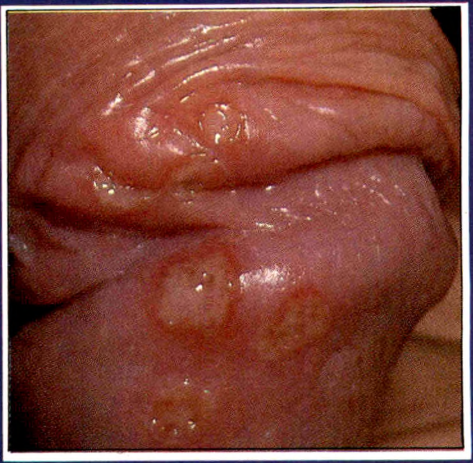

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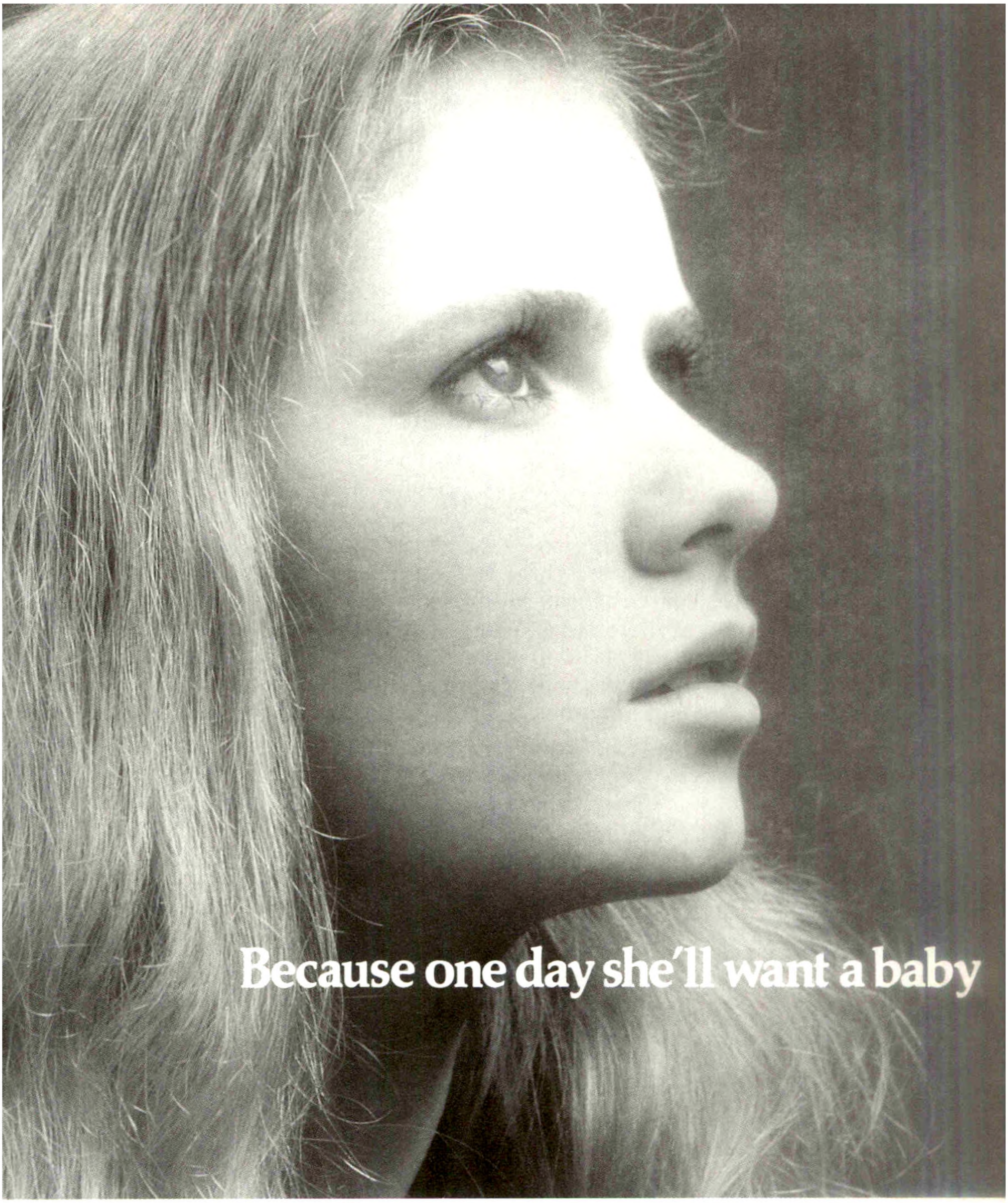
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Volume 59 · Number 7 · July 1987

Postgraduate Educational Issue – A SYMPOSIUM ON COMPLICATIONS and MEDICO-LEGAL ASPECTS OF ANAESTHESIA

Editors: G. Smith and J. Norman

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435. 3. Polson, D.W., et al., Clinical Endocrinology (1987) **26**, 205. 4.
M.M. et al., (1982) Fertil. Steril. **37**, 520. 5. Jones, G.S., et al., (198
Steril. **43**, 696.

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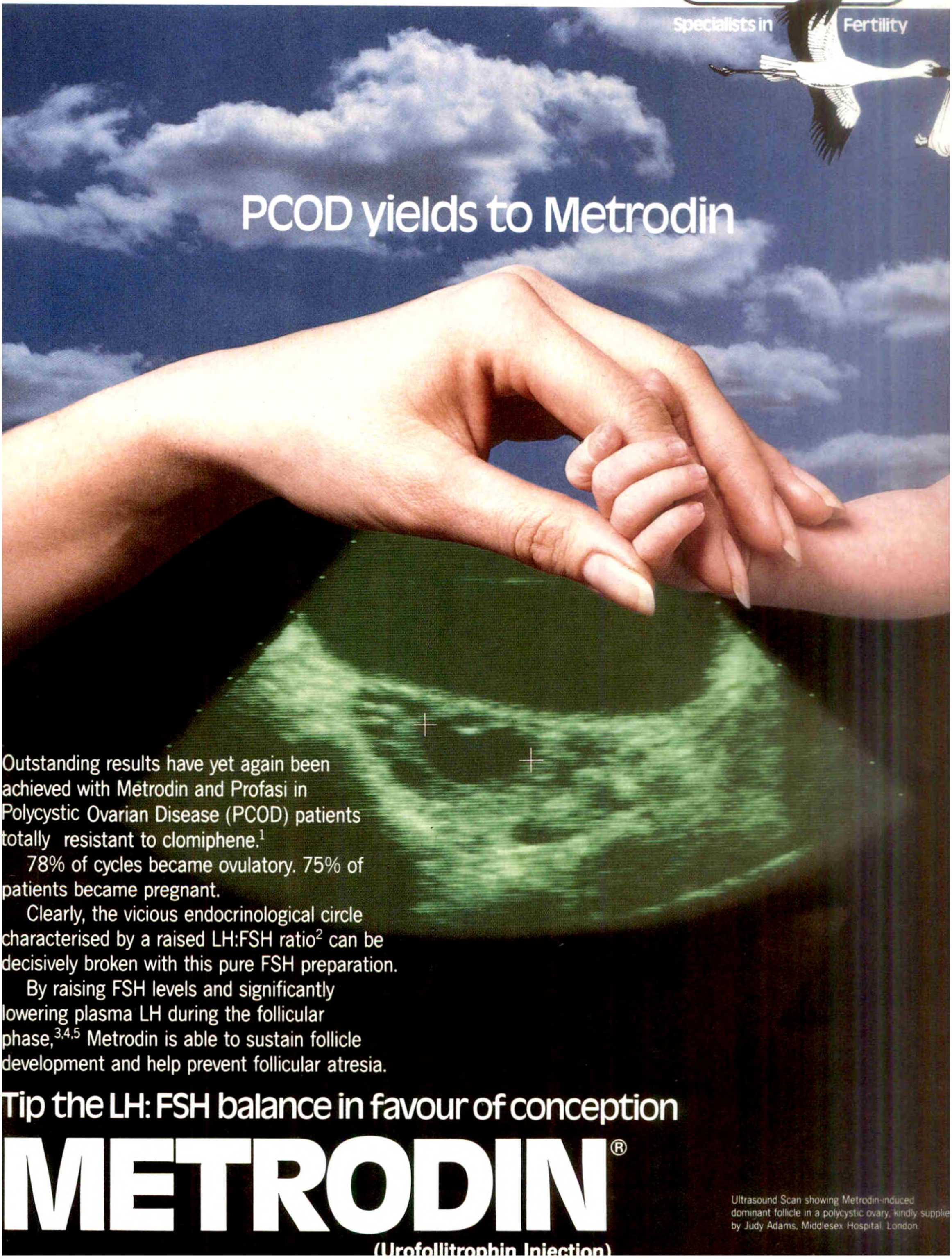

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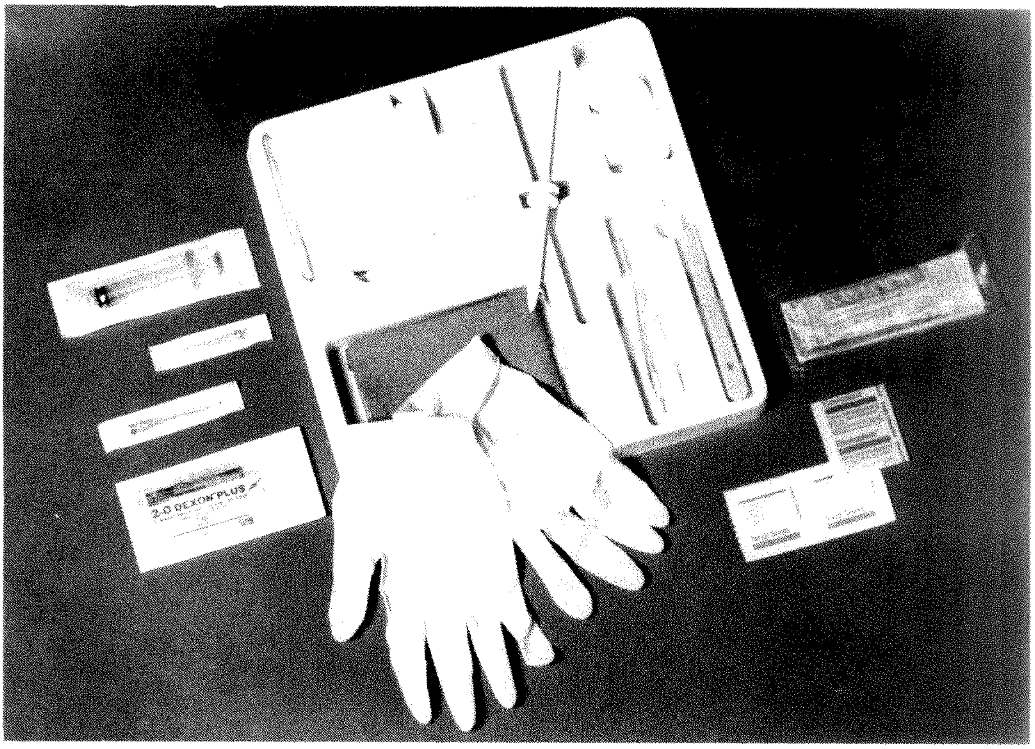

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In addition to original articles the journal includes summaries of epidemiological articles published in other journals, book reviews and annotations on topics in which the epidemiological approach is particularly apposite.

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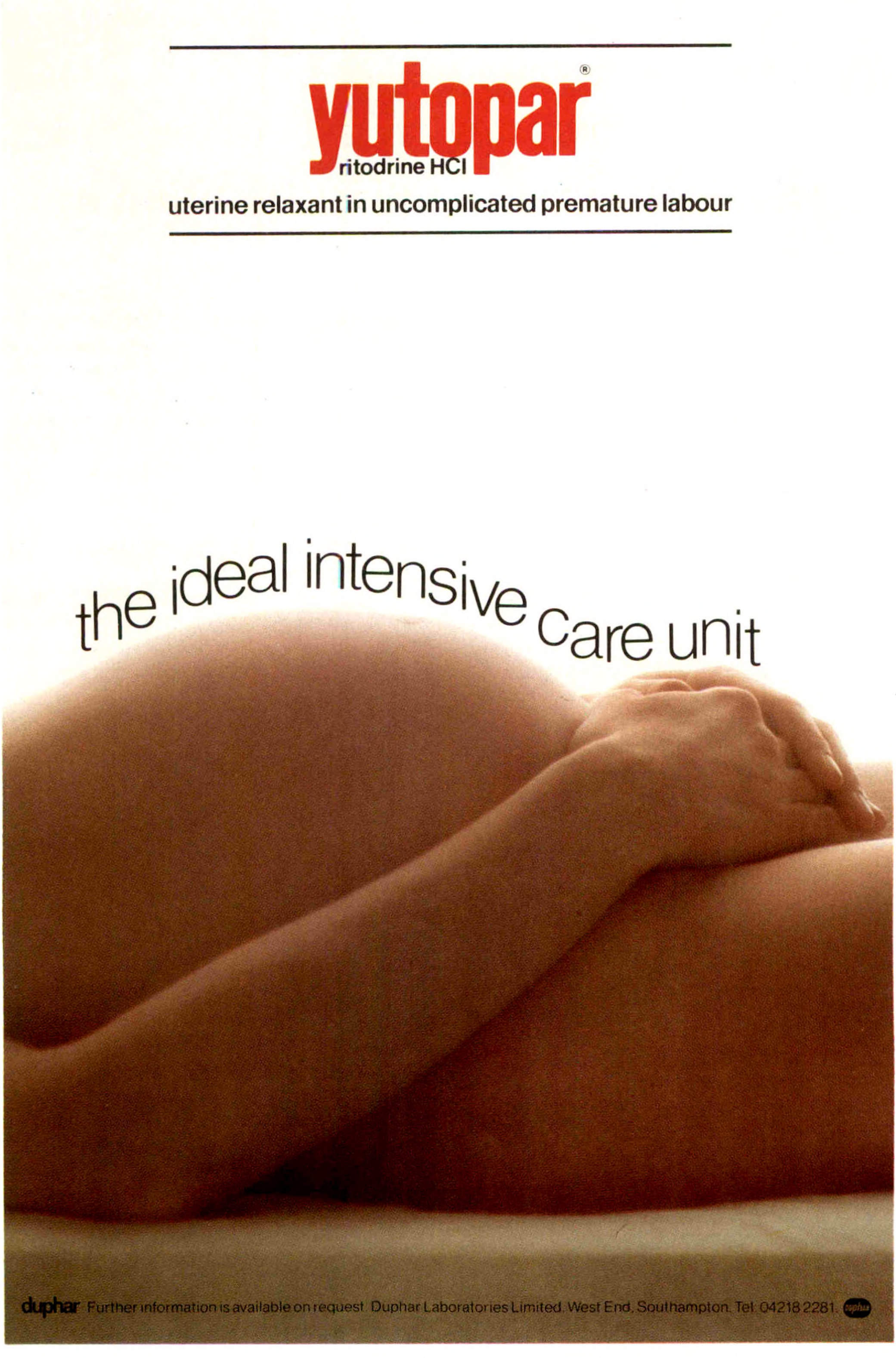

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British Journal of Obstetrics and Gynaecology
June 1988, Vol. 95, pp. 545–546

COMMENTARY

Disposal arrangements for second trimester fetuses

Since the papers by Bourne (1968) and Giles (1970) there has been an increasing interest in perinatal bereavement and more has been published on the subject. The report by the RCOG (1985) demonstrated the professional climate of opinion and the recognized need of the families who suffered such bereavement. The joint report by the Royal College of Midwives and Health Education Council (1985) emphasized the subjective involvement by the professionals in this emotive field and their need for support.

Whereas the proper management of a perinatal death is now well recognized, the emotional effect of a fetal loss before 28 weeks has received little if any attention. In this issue of the Journal (p. 547) the paper written by the combined effort of a paediatric pathologist, a chaplain and an obstetrician (in itself an illustration of the wide impact of such loss) demonstrates how some professionals are now thinking and feeling.

The aim of their investigation was to ascertain how different hospitals manage fetuses lost at between 12 and 28 weeks gestation. It is historically interesting that 'disposal' is the descriptive word used in this paper. A 'disposal' certificate was the original certificate for a stillbirth until, under professional pressure, this was changed to a 'death certificate'; 'disposal' implies something unwanted, to be got rid of, a reflection of the denigratory attitude towards a stillbirth at that time.

In this investigation, the authors were motivated by a concern for, and interest in, this otherwise totally ignored human experience, a fertile field for further study with wide implications for personal and family integrity.

Their findings from 28 hospitals speak for themselves, but what is of particular interest is the surprising information that in some six hospitals all the fetuses were buried or cremated, most hospitals had facilities for photography and special religious services, some provided blessing cards and a remembrance book and appointed a bereavement counsellor. Even more surprising was the provision of a special plot of land in some of the crematoria or cemeteries for stillbirths and second trimester fetuses.

Whilst we have come to recognize the emotional reactions to a perinatal death, the reaction to miscarriage, and how professionals could be of help, has hardly ever been examined. The size of the problem is vast and at a conservative estimate there are at least 426 000 miscarriages annually in Britain.

The situation has been highlighted by the intense controversy generated by the new Abortion Bill discussed by Parliament. Awareness of the problem is not new; 160 years ago, A. B. Granville, a physician accoucheur at the Westminster General Dispensary in London, reported a mini-survey of miscarriages (Granville 1819). Of the first 400 women he asked, 305 had miscarried and they remembered these events 'with a tenacity that nothing can relax'. Oakley *et al.* (1984) in their unique study bring home vividly the need for action on both humanistic grounds and to prevent mental ill health in the parents and the family.

One would have wished to know more of what transpired between the parents and the professionals. What sort of reactions were there to the surprising offers of a burial or a cremation, of having a photograph taken, of the choice of having prayers said at the mother's bedside or a memorial service? Above all, what is the thinking and feeling of the staff in those hospitals who offer these facilities?

In their conclusions the authors show their sensitive empathy for parents and how they see 'good obstetric practice'. They consider that their survey indicated 'that many hospitals were reviewing their procedures in the light of increased local interest and awareness of the problems'. What, I wonder, can or could be done to influence more obstetric thinking on these lines? Perhaps the RCOG might consider setting up a working party to produce guidelines as they did for perinatal deaths.

David Morris
1 Bryanston Square
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References

Batcup, G., Clarke, J. P. & Purdie, D. W. (1988) Disposal arrangements for fetuses lost in the second trimester. *Br J Obstet Gynaecol* **95,** 547-550.

Bourne, S. (1968) The psychological effects of stillbirth on women and their doctors *J R Coll Gen Pract* **16,** 103-112.

Giles, P. F. H. (1970) Reactions of women to perinatal death. *Aust NZ J Obstet Gynaecol* **10,** 207-210.

Granville, A. B. (1819) *A Report of the Practice of Midwifery at the Westminster General Dispensary during 1818.* Burgess & Hill, London.

Oakley, A , McPherson, A. & Roberts, H. (1984) *Miscarriage.* Fontana, London.

Royal College of Midwives and Health Education Council (1985) *Midwives and Stillbirth:* Report of a joint Royal College of Midwives/Health Education Council workshop held in October 1984, London.

Royal College of Obstetricians and Gynaecologists (1985) *Report of the RCOG Working Party on the Management of Perinatal Deaths.* RCOG, London.

British Journal of Obstetrics and Gynaecology
June 1988, Vol. 95, pp. 547–550

Disposal arrangements for fetuses lost in the second trimester

G. BATCUP, J. P. CLARKE, D. W. PURDIE

Summary. In 1986, 28 consultant pathologists with a special paediatric or perinatal interest in the UK and Irish Republic supplied information on current disposal methods for fetuses lost in the second trimester (12–28 weeks gestation) and the facilities available to parents. In over half the hospitals surveyed no single method of disposal was employed, but most of the fetuses were incinerated. In six hospitals all fetuses were either buried or cremated; 25 hospitals had facilities for photography and 24 made special religious services available. Other facilities available in some centres included the provision of blessing cards and a 'remembrance book' and the appointment of a bereavement counsellor. In five of the local crematoria or cemeteries a special plot of land was reserved for stillbirths and younger fetuses. The relative costs of these facilities are discussed.

Infants who are stillborn or who die in the neonatal period are issued with a stillbirth or death certificate and must, by law, be buried or cremated (Births and Deaths Registration Act 1953). There are no such requirements for fetuses born dead before 28 weeks gestational age and arrangements for the disposal of such fetuses have evolved in an *ad hoc* manner within the many hospitals throughout the country. To investigate these various arrangements, 32 consultant pathologists with a special paediatric or perinatal interest were asked in July 1986 to complete a detailed questionnaire concerned not only with fetal disposal but also with the availability of religious services and associated facilities for parents. This topic has been of concern to many in the medical field and has more recently caught the attention of the media.

Results

Of the 32 pathologists contacted, 28 replied. The geographical distribution and type of hospital or pathology department surveyed are indicated in Tables 1 and 2.

During the course of 1985, the average number of second trimester fetuses received at each centre was 101, with a wide range of 20 to 533.

Disposal

The methods of disposal are given in Table 3. In over half the hospitals surveyed no single method was employed. Although the exact proportion of fetuses in each category in any one hospital was not supplied, the questionnaire replies indicated that most of the second trimester

---

The General Infirmary at Leeds
Pathology Department, Clarendon Wing
G. BATCUP *Consultant Paediatric/Perinatal Pathologist*

Chaplain's Office
J. P. CLARKE *Hospital Chaplain*

Department of Obstetrics and Gynaecology, Clarendon Wing
D. W. PURDIE *Lecturer/Honorary Consultant*

Correspondence: Dr G. Batcup, Pathology Department, Clarendon Wing, The General Infirmary at Leeds, Belmont Grove, Leeds LS2 9NS

Table 1. Geographical distribution of hospitals and university pathology departments

England	20
Wales	1
Scotland	4
Northern Ireland	1
Irish Republic	2

Table 2. Distribution by type of hospital or pathology department

Children's hospital	6
Maternity hospital	8
University pathology department	10
District general hospital	4

Table 3. Numbers of hospitals employing various methods of fetal disposal

More than one method employed	17
Hospital incineration immediately after autopsy (method A)	9
Method A alone	1
Hospital incineration after autopsy and subsequent fixation (method B)	19
Method B alone	4
Burial or cremation (method C)	20
Method C alone	6
Preservation of some fetuses for teaching purposes	2

fetuses were incinerated within the hospital either immediately after autopsy or after a period of fixation and that, in general, only a small number of fetuses were buried or cremated, either privately or by hospital arrangement. In six hospitals, however, all fetuses were either buried or cremated. In two pathology departments, occasional malformed fetuses were permanently preserved, after removal of identity, for subsequent teaching purposes.

Photographs for parents

In 25 of the 28 hospitals, polaroid or conventional photographs of the fetus could be taken for the parents if they so desired (Table 4). In only three hospitals were photographs never taken and in two of these, large numbers of fetuses were referred from other centres.

In 12 hospitals, photographs were taken sometimes, while in 13 photography was the rule. The picture could then be given to the parents at a later date, if a request was made. Photographs were usually taken by the attending midwives and nurses, but medical staff, pathology and mortuary technicians and members of photographic departments also contributed.

Availability of special religious services

In four hospitals, none of the special religious services detailed in Table 5 was available; two of these centres received fetuses referred from elsewhere.

Prayers could be said at the mother's bedside if desired (13 hospitals), or in the hospital chapel of rest with one or both parents in attendance (19 hospitals). In three centres cremation services were possible within the hospital or its grounds. Two of these hospitals utilized their incinerator but separated the fetuses from surgical specimens and hospital waste; the chaplain was in attendance and conducted a short committal service. The third hospital possessed a separate small laboratory incinerator which was reserved solely for the disposal of these fetuses; committal services were conducted by the chaplain.

Ten hospitals arranged for cremation services in the local crematoria and a similar number held memorial services within the hospital for fetal losses that had occurred some time previously.

Other services in eight centres referred mainly to the availability of hospital-arranged burials.

Table 4. Numbers of hospitals taking polaroid or conventional photographs of second trimester fetuses for parents, subdivided according to category of photographer

		Photographs taken by			
Photographs taken	No. of hospitals	Nurses and midwives	Medical staff	Photography department	Pathology or mortuary technicians
Never	3				
Sometimes	12	7	3	4	5
Always	13	11	1	1	2

Table 5. Availability of special religious services

	No. of hospitals
No special services	4
Prayers at the mother's bedside	13
Prayers in the hospital chapel of rest with parent/s in attendance	19
Cremation service in the hospital or its grounds	3
Cremation service in the local crematorium	10
Memorial service for fetuses aborted some time previously	10
Other types of service	8

Table 6. Availability of other facilities

	No. of hospitals
Blessing card	7
Remembrance book	10
Bereavement counsellor	12
Separate hospital incinerator reserved solely for fetuses	1
Special arrangements with local crematorium or cemetery	10

Availability of other facilities (Table 6)

Christening services are appropriate only to liveborn infants, but parents of stillborn infants and younger fetuses can be offered a 'blessing card' which includes the baby's name. Seven hospitals offered blessing cards to the parents. Ten hospitals kept a 'remembrance book' in the chapel or elsewhere, in which the names of the fetuses could be recorded.

Twelve hospitals had appointed a specially designated bereavement counsellor. The questionnaire replies indicated, however, that in many hospitals where there was no counsellor, this service was provided by a team of people including midwives, medical staff and clergy.

One hospital possessed a separate small incinerator reserved solely for the disposal of aborted fetuses. Ten hospitals had made special arrangements with the local undertakers, crematorium or cemetery, most commonly with regard to fixed prices for coffins, funerals or cremations, whenever these services were arranged by the hospital. In five of the crematoria or cemeteries, a special plot of land was reserved for such fetuses and stillbirths. Two hospitals had special arrangements for communal cremation services at intervals throughout the year.

Details of burial and cremation arrangements in two hospitals are given below:

Hospital A. All first and second trimester fetuses longer than 2·5 cm are buried, after photography and a limited autopsy. Parents are offered the choice of a private or hospital burial and the cost of a hospital burial (£28.50 in 1986) is borne by a hospital fund. Within the local cemetery is a special plot of land reserved for the burial of newborn and stillborn infants and younger fetuses.

Hospital B. After autopsy, the fetuses are placed in fixative in labelled containers. Three times a year the undertakers provide a child-sized coffin and the fetuses are placed inside. The undertakers require a signed document giving the names of the fetuses and their dates of birth together with a statement that the fetuses fall within the abortion category. A cremation service is held in the local crematorium by the hospital chaplain, and hospital staff and parents may attend. The cost of each service (£140.00 in 1986) is borne by the health board. Ashes are scattered in the crematorium gardens.

Costs

Approximate costs for some of these facilities are given in Table 7.

Remembrance books are not widely available; our own is the size of a large wedding album and was specially commissioned. Polaroid cameras should include automatic focusing and close-up facilities; conventional polaroid cameras will not focus on objects less than 60 cm away. It is probably wise to advise parents that photographs will fade if permanently exposed to light, and that a negative can be obtained from the polaroid picture, enabling further prints to be made at a later date.

The special incinerator is an electrical labora-

Table 7. Approximate costs

Blessing card	Negligible
Remembrance book	£20.00
Polaroid camera and film	£120.00
Special furnace incinerator	£420.00
Private funeral or cremation	£80.00 (minimum)

tory furnace with a maximum external diameter of 48 cm and a maximum temperature of 1100°C.

Private funeral or cremation charges will vary with the wishes of the parents but are most unlikely to be under £80.00 and may well be considerably higher. The cost of a special burial plot reserved for babies will also vary with the location of the cemetery and the size of the plot required, but is likely to be in the order of thousands of pounds.

Discussion

Good obstetric practice requires a thorough knowledge by the attending staff of the correct procedures to be followed and the local facilities available for the reception and disposal of second trimester fetuses. The parents always deserve to be treated with a warm and sympathetic humanity, essential parts of which are direct and correct answers to their questions on photography, post-mortem examinations and disposal. Medical and midwifery staff should have easy access to a guide on the management of bereaved parents, detailing the locally agreed arrangements.

Growing concern by parents and hospital staff over the disposal of second trimester fetuses prompted our survey, and the results, although not necessarily representative of the country as a whole, give some indication of the facilities available over a wide area of the British Isles and Irish Republic. The survey relates to practices current in 1986 and the replies to the questionnaires indicated that many hospitals were reviewing their procedures in the light of increased local interest and awareness of the problems. The survey also relates only to those parents who either ask for a Christian service for their fetus or who raise no objection to this. Parents of different cultural backgrounds often wish to adhere to special traditions and observances, under the guidance of their own religious leader (Walker 1982).

There are several 'self-help' groups which offer considerable support to bereaved parents, amongst which the Stillbirth and Neonatal Death Society (SANDS) and its equivalent organization in Ireland are notable examples. Under the auspices of SANDS, inscribed memorial stones for babies of any age have been erected in adult cemeteries in many parts of the country.

The provision of blessing cards, remembrance book and polaroid camera should be considered in appropriate circumstances; these are not expensive items and should be available in or near all maternity units. Financing hospital cremations and burials incurs greater expense and the purchase of a burial plot may be a severe financial burden. However, collaboration between neighbouring hospitals can help to spread the cost and many centres are now considering this option.

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Reference

Walker, C. (1982) Attitudes to death and bereavement among cultural minority groups. *Nursing Times* **78**, 2106-2109.

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Smoking in pregnancy: effects of stopping at different stages

CHRISTINE MACARTHUR, E. G. KNOX

Summary. Of 4341 pregnant women, 3106 were non-smokers and 1235 were smokers at the start of pregnancy. Eighty-five had stopped smoking before 6 weeks gestation, 119 between 6 and 16 weeks, and 56 stopped after 16 weeks. A further 51 stopped temporarily and 924 smoked throughout pregnancy. The mean birthweight of the groups differed. There were also social and biological differences such as might partly explain birthweight variations so comparisons were repeated after allowing for these factors. Standardized mean birthweights were greater for all groups who stopped than for persistent smokers. Those who stopped before 6 weeks and between 6 and 16 weeks gestation had infants 217 and 213 g, respectively, heavier than the persistent smokers and similar to the non-smokers. Babies born to those who stopped after 16 weeks, or temporarily, were intermediate in weight. Appropriate advice is that stopping any time before 16 weeks is best, but stopping after this is still beneficial.

Many studies have shown that pregnant smokers have smaller babies than non-smokers, also higher rates of perinatal mortality and other adverse outcomes of pregnancy (US Surgeon General 1981). Some studies distinguished a third group, namely ex-smokers. These were usually defined as previous smokers who had stopped smoking by some arbitrary time during the pregnancy. In every series ex-smokers had heavier infants than the continuing smokers, and in most the mean birthweight was the same as for non-smokers (Lowe 1959; Frazier *et al.* 1961; MacMahon *et al.* 1966; Butler *et al.* 1972; Andrews & McGarry 1972; Schwartz *et al.* 1972; Rantakallio 1978). However, this leaves us with two problems of interpretation.

First, most of these studies defined only a single category of ex-smoker, those who stopped by *X* weeks, so that the effects of stopping at different stages were not investigated. It is therefore not clear whether there is real benefit from stopping immediately after conception or, conversely, whether stopping later in pregnancy is too late to have an effect. Second, smokers who stop earlier in pregnancy may differ from those who stop later and from non-smokers and persistent smokers, in terms of some of the social and biological characteristics which influence birthweight. There is indeed some evidence that they do differ (Andrews & McGarry 1972; Schwartz *et al.* 1972; Rantakallio 1978; Donovan 1977).

The object of this present study was to repair these deficiencies and examine the effect on birthweight of stopping smoking at different stages of pregnancy, taking into account inter-related social and biological characteristics.

Patients and methods

The study was based on all white European women who booked and subsequently were

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Health Services Research Centre, Department of Social Medicine, Medical School, Edgbaston, Birmingham B15 2TJ
CHRISTINE MACARTHUR *Research Fellow*
E. G. KNOX *Professor*

Correspondence: C. MacArthur

delivered at a West Midlands maternity hospital over a 12-month period, and who said they had been smokers at the start of pregnancy ($n=1434$). The sample was recruited at the time of the hospital booking visit and an initial statement of smoking behaviour was recorded. Interviews took place in hospital, after delivery, when information was obtained about smoking throughout pregnancy and about other relevant items. Information about the sex of baby, birthweight, gestation at delivery, maternal height, age, parity and social class was extracted from case notes. Of the 1434 women, 199 were not interviewed; either they were discharged early ($n=10$), or medical problems made an interview not feasible ($n=16$), or a change in surname prevented an immediate link with the recruitment record on admission ($n=158$). For 15 the case notes could not be traced. The remaining 1235 (85%) were included in the final analysis.

The white European women who booked at the hospital during the same period and who were non-smokers at the start of pregnancy ($n=3106$) were not interviewed, but comparable case note information was obtained.

Statistics

Statistical analyses and birthweight standardization used the Statistical Package for Social Scientists (SPSS). 'Expected' birthweights were calculated from a multiple regression equation, whose coefficients were from the whole group of women who had been smokers at the start of pregnancy.

Results

Categories of smoking behaviour

The 1235 women who were smokers at the start of pregnancy were classified into five groups based on smoking behaviour during pregnancy. The first three groups stopped smoking at different stages of pregnancy and did not start again before delivery; the fourth stopped but started again later and the fifth smoked throughout.

Early stoppers. These 85 women stopped smoking during the first 6 weeks gestation. Most stopped as soon as they knew they were pregnant. Mean gestation at stopping was 5 weeks. The mean daily number smoked before pregnancy was 13·8 cigarettes.

Intermediate stoppers. These 119 women stopped between 6 and 16 weeks gestation. Mean gestation at stopping was 10 weeks. The mean daily number of cigarettes smoked before pregnancy was 13·6.

Late stoppers. These 56 women stopped after 16 completed weeks gestation. All but five had stopped before 28 weeks, four stopped after 28 weeks and one after 29 weeks gestation. Mean gestation at stopping was 22·5 weeks. The mean daily number of cigarettes smoked before pregnancy was 13·1.

Temporary stoppers. These 51 women stopped smoking during pregnancy but started again before delivery. Most stopped quite early: 30 during the second month and 18 during the third month. The mean duration of abstinence was 12·5 weeks. Mean daily consumption on restarting was 7·5 cigarettes. Before pregnancy, mean daily cigarette consumption was 15·5.

Persistent smokers. These 924 women continued to smoke throughout pregnancy. Mean pre-pregnancy cigarette consumption was 18·6 per day, significantly higher than in all the other groups. Some women in this group reduced their smoking; mean daily number smoked after booking was 13·1.

Comparison of maternal characteristics

Several of the social and biological characteristics which are known to be associated with birthweight, namely maternal age, height, social class, and parity (Knox *et al.* 1986) differed according to smoking behaviour (Table 1).

Those who stopped before 6 weeks or between 6 and 16 weeks were older, taller, of higher social class and included more nulliparae than the persistent smokers and resembled the non-smokers in these respects. With the exception of parity these differences would lead us to expect bigger babies irrespective of the smoking differences.

By contrast, late stoppers (after 16 weeks) were similar in maternal age, height and social class to those who smoked throughout pregnancy, so these two groups would be expected to have similar size babies. Any observed birthweight excess among the stoppers might be more confidently attributed to the different smoking patterns. Indeed, the group who stopped after

Table 1. Characteristics of the women in the six categories of smoking behaviour

	Smoking category					
Variable	Non-smokers (n=3106)	Stopped by 6 weeks (n=85)	Stopped between 6 and 16 weeks (n=119)	Stopped after 16 weeks (n=56)	Temporary stoppers (n=51)	Persistent smokers (n=924)
Maternal age (years)*	27·3	27·4	26·4	24·7	26·4	25·3
	(0·09)	(0·57)	(0·53)	(0·67)	(0·67)	(0·17)
Height (cm)*	161·6	163·1	162·3	161·0	161·5	160·9
	(0·11)	(0·63)	(0·64)	(0·81)	(0·80)	(0·21)
	(n=2998)	(n=83)	(n=118)	(n=54)	(n=49)	(n=890)
Social class I/II (%)	25	24	23	12·5	22	11
Nulliparous (%)*	46	54	61	50	51	38
Gestation at booking (weeks)	NK	12·9	12·9	17·2	12·6	15·4
		(0·37)	(0·28)	(0·68)	(0·48)	(0·18)
Smoking before pregnancy (cigarettes/day)	None	13·8	13·6	13·1	15·5	18·6
		(0·89)	(0·81)	(1·21)	(1·13)	(0·28)
Gestation at delivery (days)*	278·2	277·8	279 7	278·5	277·1	276·5
	(0·24)	(1·44)	(1·14)	(1·95)	(1·56)	(0·46)
Percentage male babies*	52	52	65	50	39	50 5

Results are mean (SE) where appropriate.
NK, Not known.
*These variables were taken into account in the birthweight standardization procedures.

16 weeks contained more nulliparae than did the persistent smokers, and this would have predicted a *lower* birthweight among these stoppers.

The temporary stoppers were intermediate between those who had stopped by 16 weeks and the persistent smokers. There were more social class I and II women among the temporary stoppers: they were older and more were having their first baby. But there was no difference in maternal height.

Birthweight comparisons

The crude mean birthweights for all the groups are shown in row 1 of Table 2. All the groups

Table 2. Birthweights in the six categories of smoking behaviour*

	Non-smokers (n=2998)	Stopped by 6 weeks (n=83)	Stopped between 6 and 16 weeks (n=118)	Stopped after 16 weeks (n=54)	Temporary stoppers (n=49)	Persistent smokers (n=890)
Birthweight (g)						
Observed	3382·42	3404·34	3439·49	3324·48	3242·65	3140·25
	(10·02)	(63·44)	(50·84)	(57·15)	(67·66)	(17·63)
Expected	3222·79	3232·98	3271·87	3250·46	3176·78	3185·76
	(6·32)	(39·04)	(31·08)	(41·69)	(41·39)	(11·76)
Excess	+159·63	+171·36	+167·62	+74·02	+65·87	−45·52
	(7·73)	(45·30)	(39·16)	(51·70)	(59·83)	(13·46)
Significance compared with persistent smokers	<0·001	<0·001	<0·001	<0·05	<0·06	
Mean duration of abstinence (weeks)	40	35	30	17·5	12·5	

Results are means (SE).
*Women for whom height was not known are excluded.

who stopped, as well as the non-smokers, had bigger babies than the persistent smokers, although the 102 g excess for the temporary stoppers was not statistically significant.

Birthweight was next standardized for maternal age, height and parity, gestation at delivery and sex of the child in order to allow for the known associations with these factors. Indirect standardization, as used, resulted in 'expected' values in each of the groups (row 2 of Table 2) and a calculated 'excess' of observed over expected (row 3 of Table 2).

These analyses confirmed the non-standardized findings that all the groups who stopped smoking had heavier babies than those who smoked throughout pregnancy. Babies of women who stopped before 6 weeks were similar in weight to those who stopped between 6 and 16 weeks: they were 217 g and 213 g, respectively, heavier than infants of persistent smokers (i.e. an excess birthweight of 171 and 168 g compared with a deficit of 46 g). Those who stopped after 16 weeks were intermediate: the infants were 120 g heavier than the persistent smokers and 100 g lighter than the babies of those who stopped before 16 weeks. The group who stopped temporarily had babies 111 g heavier than the persistent smokers: they were similar in size to the late stoppers.

In addition to standardizing birthweight for the various confounding factors, we also noted that the group of late stoppers were identical in their other maternal characteristics to the persistent smokers (except for parity which would have a negative effect) yet still had significantly heavier infants. These findings support the conclusion that the birthweight differences result from smoking behaviour and not the social and maternal differences.

Table 2 shows that stopping smoking at any time up to 30 weeks results in increased birthweight. The greatest effects result from stopping before 16 weeks. Stopping very early in the first few weeks has no additional effect.

Discussion

The anti-smoking advice supplied in leaflets to pregnant women in the UK is based largely upon the results of the extensive British Perinatal Mortality Study (Butler *et al.* 1972). Ex-smokers in this study were defined as those who had stopped by the fourth month, and their birthweights were the same as for non-smokers. It might therefore be concluded that provided a woman stops smoking by this time, her infant will suffer no harm. However, there was no comparison of women who stopped earlier or later within this 4-month period, and none between those who stopped after 4 months and those who had smoked throughout. There is therefore no basis for advising whether cessation at 2 months is better than cessation at 4 months or, for a woman still smoking after 4 months, whether it is now worth stopping.

Most other published studies likewise failed to resolve these points of practical detail; and mainly for the same reason. All but one of them defined only a single category of ex-smoker. Different studies chose different gestational definitions of ex-smokers, but there were no systematic variations of birthweight effect according to this choice. For Lowe (1959) ex-smokers were those who had stopped by the end of the fifth month (with a few exceptions); for Schwartz *et al.* (1972), in France, they were those who stopped by the end of the third month. Frazier *et al.* (1961) defined them as smokers who had stopped by the time of interview and for 60% this was during the second trimester and for 32% it was during the third. MacMahon *et al.* (1966) defined ex-smokers as those who stopped immediately before but not during pregnancy and Andrews & McGarry (1972) included women who gave up either before or during the early part of pregnancy. In a Finnish study by Rantakallio (1978) ex-smokers were those who stopped between the second and sixth months.

Only one investigation, apart from our own, used multiple ex-smoker classes. Rush & Cassano (1983), using information collected as part of the 1970 British Births Survey, compared (a) smokers who stopped in the first month, (b) those who stopped between 2 and 6 months, (c) those who stopped between 7 and 8 months, and (d) those who stopped in the ninth month. They found no difference between the first three categories, all of which had similar mean birthweights to the non-smokers. Only the fourth category, women who stopped in the ninth month, had a mean birthweight not significantly different from those who smoked throughout. Apart from this, they found no gradient according to time of stopping.

Our own study agrees that women who stopped at any time up to 30 weeks (no one stopped after this) had heavier infants than persistent smokers. It also confirmed that provided a woman stopped before 16 weeks, the exact timing made little or no difference to birthweight. It differed in showing that infants of late stoppers and temporary stoppers were intermediate in birthweight. Although the infants were smaller than for early stoppers, the hazards of continual smoking were significantly diminished.

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References

Andrews, J. & McGarry, J. M (1972) A community study of smoking in pregnancy. *J Obstet Gynaecol Br Commonw* **79**, 1057-1073.

Butler, N. R., Goldstein, H & Ross, E M. (1972) Cigarette smoking in pregnancy: its influence on birthweight and perinatal mortality. *Br Med J* **ii**, 127-140

Donovan, J W. (1977) Randomised controlled trial of anti-smoking advice in pregnancy. *Br J Prev Soc Med* **31**, 6-12.

Frazier, T. M., Davis, G. H., Goldstein, H & Goldberg, I. D. (1961) Cigarette smoking and prematurity: a prospective study. *Am J Obstet Gynecol* **81**, 988-996.

Knox, E. G., Lancashire, R. & Armstrong, E H (1986) Perinatal mortality standards: construction and use of a health care performance indicator *J Epidemiol Community Health* **40**, 193-204

Lowe, C. R. (1959) Effect of mothers' smoking habits on birthweight of their children. *Br Med J* **iii**, 673-676.

MacMahon, B , Alpert, M. & Salber, E. J (1966) Infant weight and parental smoking habits *Am J Epidemiol* **82**, 247-261

Rantakallio, P. (1978) The effect of maternal smoking on birthweight and the subsequent health of the child. *Early Hum Dev* **2**, 371-382

Rush, D & Cassano, P (1983) Relationship of cigarette smoking and social class to birthweight and perinatal mortality among all births in Britain, 5-11 April 1970. *J Epidemiol Community Health* **37**, 249-255.

Schwartz, D., Goujardi, J , Kaminski, M & Rumeau-Rouquette, C. (1972) Smoking and pregnancy. Results of a prospective study of 6989 women *Eur J Clin Biol Res* **XVII**, 867-879.

US Surgeon General (1981) *The Health Consequences of Smoking for Women.* Department of Health and Human Services, Washington, pp. 189-239.

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Is routine antenatal booking vaginal examination necessary for reasons other than cervical cytology if ultrasound examination is planned?

PETER O'DONOVAN, JANESH K. GUPTA, JOHN SAVAGE,
JAMES G. THORNTON, RICHARD J. LILFORD

Summary. Sixteen ovarian cysts, including one borderline ovarian malignancy, and ten trichomonal vaginal discharges but no cases of cervical incompetence or ectopic pregnancy had been detected at booking vaginal examination in 11 622 consecutive antenatal case records abstracted retrospectively. In an attitude survey of pregnant women 77% believed that vaginal examination was reassuring, 55% found it unpleasant, and 18% thought it could cause miscarriage. This, and a review of the literature, suggests that routine vaginal examination if ultrasound is planned has few advantages beyond the taking of a cervical smear.

Some traditional obstetric procedures, although ineffective, are innocuous and may have a ritual function. Routine vaginal examination at the first antenatal attendance, however, requires reappraisal because it is widely perceived as intrusive and unpleasant. Advocates should establish that treatable conditions are detected sufficiently frequently to make it worthwhile when other diagnostic methods such as ultrasound are to be used.

The following advantages of vaginal examination at the booking antenatal examination may be proposed: (i) The detection of ovarian tumours and ectopic pregnancies; (ii) assessment of uterine size which may alert the examiner to the possibility of multiple or molar pregnancy; (iii) the discovery of cervical dilatation which may lead to measures to prevent premature labour or miscarriage.

The advantages of taking a cervical smear may be added but these have been discussed elsewhere (Lee *et al.* 1981) and here we shall examine the possible advantages of routine vaginal examination if a recent smear was satisfactory and it is not planned to repeat it. Our discussion will also assume that ultrasound examination is planned.

Patients and methods

The first part of the study involved a review of 11 622 consecutive deliveries at a large British teaching hospital, the General Infirmary at Leeds (LGI). The findings of the vaginal examination at the booking (first antenatal) visit were reviewed and where any positive features were recorded the subsequent action, diagnosis and

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Department of Obstetrics and Gynaecology, Clarendon Wing, The General Infirmary at Leeds, Leeds LS2 9NS
PETER O'DONOVAN *Registrar*
JAMES G THORNTON *Research Fellow*

Leeds University
JANESH K. GUPTA *Medical Student*

Leeds Polytechnic
JOHN SAVAGE *Statistician*

Department of Obstetrics and Gynaecology, St James's University Hospital, Leeds LS9 7TF
RICHARD J. LILFORD *Professor*

Correspondence. Professor R. J. Lilford

outcome were noted. Details were also obtained independently from the cancer registry, pathology reports and theatre records of all patients with ovarian cysts diagnosed during pregnancy by other means (subsequent examination, ultrasound or at operation) and of all patients who had cervical cerclage performed in pregnancy. We were able therefore to determine the proportion of ovarian neoplasms discovered by vaginal examination and of cervical cerclage operations influenced by the vaginal findings.

In the second part of the study, a two-part questionnaire was administered to 201 antenatal patients. The first part of the questionnaire consisted of six statements (Table 1) about vaginal examination with the subject's responses recorded on a Likert scale. In the second part, the women were asked to rate their perception—between completely intolerable and insignificant—on an ungraded visual analogue scale, of vaginal examination, dental examination, dental filling, venesection, urethral catheterization, motorway breakdown, and rectal examination. The questionnaires were completed in private with one of two authors (J.K.G. and P.O'D.) available to answer questions and formed part of a larger study of the methodology of obtaining patients' values to be reported separately. Each author administered an equal number of questionnaires in each of the two large city hospitals.

Results

Analysis of case records

Vaginal examination findings were recorded in 11 270 of the 11 622 (97%) records reviewed. Sixteen adnexal cysts were detected clinically and 14 of these were later also detected on scan. In total 57 ovarian cysts were diagnosed but 40 of these were only detected by ultrasound scan. One undiagnosed Stage IA ovarian carcinoma of borderline malignancy was found incidentally at caesarean section. Ten other patients had surgery eventually and two follicular, one luteal, one broad ligament and two dermoid cysts, and one fibroid, one cystadenoma and one Stage 1A serous cystadenoma of borderline malignancy were removed; in one patient no tumour was found.

In no woman was cervical dilatation or effacement noted on vaginal examination, nor did the cervical condition ever lead to cerclage or any other management to prevent premature labour. Cervical sutures were inserted in 37 women always on the basis of the previous history. There were 120 multiple pregnancies during the study period and 11 were suspected on the original vaginal examination, including one set of triplets. Vaginal discharge was noted in 110 women and microbial culture identified pathogenic organisms in 51 (10 trichomonas and 41 candida). Condylomata acuminata was discovered in five women and four of them had cautery performed. No ectopic pregnancies were suspected on the basis of routine examination.

Table 1. Attitude questionnaire

Vaginal examination at the first antenatal attendance (booking clinic):
- (a) reassures that everything is well
- (b) should be part of routine examination
- (c) is *not* unpleasant
- (d) is unpleasant
- (e) may cause some people to delay reporting pregnancy
- (f) may cause miscarriage

Responses were recorded on a Likert scale as 'strongly agree, agree, neutral, disagree or strongly disagree'.

Attitudes to vaginal examination

The Likert scale of patients' attitudes showed that 77% believed that vaginal examination was reassuring and 52% thought that it should be part of a routine examination, but 55% found it unpleasant. Overall 45% felt that some women might delay attending hospital for fear of vaginal examination and 18% felt that it might cause miscarriage. On the visual analogue scale patients ranked vaginal examination slightly better than a dental filling or rectal examination but worse than catheterization, dental examination or venesection.

Discussion

The main fetal advantage claimed for vaginal examination is the possibility of preventing premature labour by insertion of a cervical suture following detection of a dilating cervix. This is unlikely to be effective (Rush *et al.* 1984), although the results of the large randomized trial are awaited. Unnecessary cervical suture may be harmful and few obstetricians insert them on the basis of cervical changes alone. Modification of lifestyle and other forms of social manipulation in patients at high risk of premature labour have been advocated (Papiernik *et al.* 1986) on the basis of uncontrolled data. Cervical changes feature on the list of risk factors for premature labour but their significance is much less than other features such as a previous history of miscarriage or bleeding in early pregnancy. It is much easier to predict premature labour than to prevent it. It is unlikely anyway that a single cervical assessment would be beneficial, and Papiernik *et al.* (1986) himself recommended serial examination. The hypothesis that premature labour may be prevented by modification of lifestyle is unproven and the economic and other opportunity costs of this advice suggest that it is not warranted. Other possible fetal advantages of routine vaginal examination depend on demonstration of inappropriate uterine size for gestational age and cannot be sustained if ultrasound examination is planned.

The most compelling maternal indication for vaginal examination in pregnant women with a recent satisfactory smear test would be demonstration that early malignant ovarian tumours are detected with sufficient frequency to make the procedure worthwhile. We have, therefore, made an assessment of the frequency with which curable ovarian malignancy, missed on ultrasound, would be detected as a result of vaginal examination. The incidence of malignant ovarian tumours throughout the reproductive age group is 6 to 7 per 100 000 (Bennington *et al.* 1968). One borderline ovarian malignancy was discovered on vaginal examination among nearly 12 000 patients in this series. Morrow (1981) confirms that borderline tumours are relatively more common amongst younger women and account for 83% of all primary malignant ovarian tumours between the ages of 20 and 29 years and 67% between the ages of 30 and 39 years. Hogston & Lilford (1986) detected one malignant tumour amongst 26 000 ultrasound scans, 137 of which revealed an adnexal mass, while Thornton & Wells (1987) found one frankly malignant and six borderline ovarian tumours in 45 000 pregnancies. The present study shows that ultrasound picks up four times as many ovarian neoplasms compared with vaginal examination and if used alone will detect more than three quarters in pregnancy because many clinical lesions were also detected on ultrasound. Thus, vaginal examination (assuming a rate of carcinoma of 1 in 20 000) might pick up one extra malignant tumour in 80 000 women or less. In many the tumour would be incurable or, in the case of borderline tumours, would have been detected and cured later. Thus the life-saving potential of routine vaginal examination, if ultrasound scan is to be performed, is likely to be considerably less than 1 in 100 000.

The advantages of detecting curable ovarian cancer as infrequently as this must be balanced against distaste for the procedure. A number of studies (Hamilton & Dodge 1981; Osofsky 1967; Haar *et al.* 1977) have looked at women's reactions to vaginal examination in the gynaecological clinic and showed that it is an intrusive and unpleasant experience. Our study is the first to assess the attitudes of pregnant women and our findings confirm that it is a moderately distasteful procedure. It is noteworthy that a sizeable proportion of subjects felt that women might delay reporting their pregnancy because of fear of internal examination and that some believed that miscarriage could be provoked in this way. Nevertheless, the fact that women dislike vaginal examination does not mean that it should not be carried out gently and with reassurance that it does not cause miscarriage. We would have liked to obtain a direct estimate of the diagnostic benefits that patients would offset against the perceived disadvantages of vaginal examination but a pilot experiment showed that very few patients were able to comprehend this difficult cost-benefit decision.

Another possible reason for performing routine vaginal examination is to detect non-malignant ovarian cysts which may undergo complications such as torsion in pregnancy. This benefit must, however, be offset against the unnecessary surgery following false-positive findings (Hogston & Lilford 1986). Ultrasound criteria have been developed to maximize the chance of diagnosis of neoplastic cysts while minimizing intervention for purely functional changes (Hogston & Lilford 1986; Lilford *et al.* 1979). The net gain from vaginal examination for this purpose, given that torsion is rare, and unnecessary surgery in pregnancy undesirable, must be very small. The detection of ectopic gestation is another possible advantage of vaginal examination. The sensitivity of vaginal examination in detecting asymptomatic lesions before tubal rupture is certainly low and ultrasound examination is a far more appropriate method of confirming intrauterine gestation. From our review the only clear benefit was the detection of trichomonal vaginal discharge in 10 women (0·1%) although it is not clear how many of these would have admitted to this symptom.

We therefore conclude that routine vaginal examination in pregnancy, assuming that an ultrasound scan is intended, has no fetal benefit. The possibilities of detecting a malignant ovarian tumour in time for a cure, along with other possible maternal advantages, are so remote that they fall well below the risks to which we are all exposed in our daily lives. If people were truly so risk adverse then many of the daily activities which we take for granted would be precluded (Inman 1984). Some obstetricians might argue that it should be recommended because they regard the low return as worthwhile or because many women expect to have an examination and find it reassuring. Many others, including the authors, no longer do so because the likely benefits are so small. Either way, an inflexible and unyielding approach cannot be justified.

References

Bennington, J. L., Ferguson, B. R. & Haber, S. L. (1968) Incidence and relative frequency of benign and malignant ovarian neoplasms. *Obstet Gynecol* **32**, 627-632.

Haar, E., Halitsky, V. & Stricker, G. (1977) Patients' attitudes towards gynecologic examination and to gynecologists. *Med Care* **15**, 787-795

Hamilton, M. S & Dodge, E. F. (1981) Pelvic examination: patient safety and comfort. *JOGN Nurs* **10**, 344-345.

Hogston, P. & Lilford, R J. (1986) Ultrasound study of ovarian cysts in pregnancy. prevalence and significance. *Br J Obstet Gynaecol* **93**, 625-628

Inman, W. H W (1984) *PEM News* August 2, 16.

Lee, R. B., Neglia, W. & Park, R G (1981) Cervical carcinoma in pregnancy *Obstet Gynecol* **58**, 584-589.

Lilford, R J., Kukard, R F. P., Coetzee, E. J. & Davey, D. A (1979) The use of ultrasound in the diagnosis of pelvic masses. *S Afr Med J* **56**, 27.

Morrow, C P. (1981) Malignant and borderline epithelial tumors of ovary: clinical features, staging, diagnosis, intraoperative assessment and review of management In *Gynecologic Oncology* (Coppleson, M., ed.), Churchill-Livingstone, Edinburgh, pp. 655-679.

Osofsky, H. J. (1967) Women's reactions to pelvic examination. *Obstet Gynecol* **30**, 146-151

Papiernik, E., Bouyer, J., Collin, D , Winisdoerffer, G. & Dreyfus, J (1986) Precocious cervical ripening and preterm labor. *Obstet Gynecol* **67**, 238-242

Rush, R. W., Isaacs, S., McPherson, K., Jones, L , Chalmers, I & Grant, A (1984) A randomized controlled trial of cervical cerclage in women at risk of spontaneous preterm delivery *Br J Obstet Gynaecol* **91**, 724-730.

Thornton, J. G. & Wells, M. (1987) Ovarian cysts in pregnancy: does ultrasound make traditional management inappropriate? *Obstet Gynecol* **69**, 717-721

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Factors affecting the uptake of screening for neural tube defect

DOROTHY KYLE, CAROLE CUMMINS, STUART EVANS

Summary. A questionnaire concerning pregnant women's knowledge of, and attitudes to, serum alpha fetoprotein (AFP) screening for spina bifida was sent to all pregnant women receiving a health education leaflet on AFP screening who booked at the Birmingham Maternity Hospital in the first quarter of 1984. The majority said that they would accept the test, and subsequently did so. This suggests that low uptake of the test is not a result of patients' resistance, and the results indicated that the provision of early information about the test is likely to improve uptake and decrease anxiety. With the increasing clinical usefulness of the AFP test, routine screening of pregnant women with an 'opt-out' system is becoming clinically desirable, and the survey suggests that it would be acceptable to the patients.

A serum alpha fetoprotein (AFP) screening service is available for all pregnant women in the West Midlands Regional Health Authority, yet in 1984 only about half of them were tested.

To determine how far poor uptake was related to the patient's behaviour and patient's resistance, it was decided to survey pregnant women's attitudes to, and knowledge of, screening for neural tube defects. It was expected that this would also suggest ways in which the organization and timing of screening might promote uptake.

Central Birmingham Health Authority, District Office, Vincent Drive, Edgbaston, Birmingham B15 2TZ
DOROTHY KYLE *Specialist in Community Medicine*

Health Services Research Centre, Department of Social Medicine, University of Birmingham, Edgbaston, Birmingham B15 2TJ
CAROLE CUMMINS *Research Associate*

Birmingham Maternity Hospital, The Queen Elizabeth Medical Centre, Birmingham 15
STUART EVANS *Principal Biochemist*

Correspondence: Dorothy Kyle

Patients and methods

All 1235 patients booking at the Birmingham Maternity Hospital in the first quarter of 1984 who were sent the standard leaflet about AFP screening (West Midlands Regional Health Authority Public Relations Department. *Screening for Spina Bifida*) were also sent a questionnaire designed both to explore their attitudes to and knowledge of screening for neural tube defects and also to assess the value of the leaflet. They were asked to hand the completed questionnaire to the booking clerk on their booking attendance. When the questionnaires were returned, the clerk was usually able to attach a patient identification label to the envelope which enabled questionnaires to be linked to AFP test records for 1984. As the questionnaires were collected at the first hospital visit, the women's answers were not influenced by anything that they heard at hospital during their current pregnancies. Overall, 957 questionnaires were returned, a response rate of 77·5%. Percentages in the text and tables refer to respondents to specific questions: response rates to individual questions were invariably high.

Results

Prior knowledge about spina bifida and screening test

Nearly all the women, 95%, had heard of spina bifida and 73% had heard that there was a screening test available for it. Women from higher social classes (using the woman's own occupation) were significantly more likely to have heard of spina bifida screening. Overall, 87% of social classes I and II had heard of a screening test, compared with 73% of social class III non-manual workers and 63% of social classes IV and V ($\chi^2_2=31{\cdot}38$, $P<0{\cdot}001$).

Of women who had had a previous pregnancy, 77% had heard about the screening test compared with 67% of those who had not been pregnant before ($\chi^2_1=10{\cdot}71$, $P<0{\cdot}01$).

Only 41% of women who had had a previous pregnancy said that they had heard about the screening test from a medical source. Among primigravidae only 9% said that they had heard about screening from a medical source, although all must have seen their general practitioner before booking.

Response to the leaflet

Nearly all the women, 98%, found the leaflet clear and easy to understand. Half said that they found it very helpful and only 2% found it unhelpful, even though 27% said that the leaflet had told them nothing that they did not know already.

The leaflet was most effective in giving information to women in routine non-manual or manual jobs. Around 27% of both routine non-manual workers and manual workers said that the leaflet contained nearly all new information, compared with 11% of social classes I and II ($\chi^2_4=40{\cdot}54$, $P<0{\cdot}001$).

Acceptance of screening

Overall, 98% of the women thought that screening in pregnancy for spina bifida was a good idea. The leaflet had a positive influence in favour of screening: 9% who thought that screening was a good idea said they had come to this decision only after reading the leaflet.

Only 5% said that they would definitely not accept AFP screening and 78% said they would definitely accept screening (Table 1).

Of the respondents 92% thought that they had enough information to decide whether or not to accept the screening test. Of those who were definitely not going to accept the test, 22% also said that they did not have enough information to make a decision and 20% of the women who were still making up their minds also stated that they did not have enough information to decide. The quality of information about the test appears to affect its acceptability: there was a significant association between having enough information to make a decision and a definite acceptance of the test ($\chi^2_1=133{\cdot}84$, $P<0{\cdot}001$).

The woman's religion was expected to have an influence on acceptance of the test because of the possibility of termination of pregnancy. Church of England and Roman Catholic women comprised 77% of the respondents. Although significantly more Church of England women than Roman Catholic women said they would definitely accept the test ($\chi^2_1=3{\cdot}91$, $P<0{\cdot}05$), a majority of the Catholic women still said that they would definitely accept the screening test. Only 7% of Catholics definitely did not want it (Table 1).

Feelings about termination

The women were asked whether, in the unlikely event of their babies having spina bifida, they would be prepared to have the pregnancy termi-

Table 1. Intentions regarding the screening test

	Intentions of accepting the screening test				
	Definitely yes *n* (%)	Definitely no *n* (%)	Need more information *n* (%)	Still making up mind *n* (%)	Total
Church of England	486 (82)	18 (3)	31 (5)	59 (10)	594
Roman Catholic	109 (74)	10 (7)	9 (6)	19 (13)	148
All respondents	742 (78)	47 (5)	54 (6)	107 (11)	950

nated. A little over half the women said that they would, while a further 36% said that they did not know. Only 9% of the respondents said that they would not have the pregnancy terminated.

Although there was a highly significant difference in the proportions of Roman Catholic and Church of England women who were not prepared to have the pregnancy terminated ($\chi^2_1=9\cdot51$, $P<0\cdot01$), only 11% of the Catholics said they would not be prepared to have a termination (Table 2). Of the minority religious groups only Jehovah's Witnesses stood out; all six would refuse termination.

Table 2. Views on termination if baby had spina bifida in different religious groups

	Prepared to have the pregnancy terminated if baby had spina bifida		
Religion	Yes n (%)	No n (%)	Don't know n (%)
Church of England	368 (62)	24 (4)	198 (33)
Roman Catholic	63 (43)	16 (11)	67 (45)
Non-Conformist	23 (53)	8 (19)	12 (28)
Methodist	13 (65)	2 (10)	5 (25)
Other Christian	7 (28)	9 (36)	9 (36)
Sikh	9 (31)	3 (10)	14 (48)
Muslim	6 (25)	5 (21)	11 (46)
Hindu	3 (19)	3 (19)	10 (63)
Jehovah's Witness	0 —	6 (100)	0 —
Other religions given	0 —	3 (50)	3 (50)
Agnostic/atheist/no religion	18 (78)	1 (4)	4 (17)
Total	520	82	338

Table 3. Factors associated with anxiety on receiving the leaflet

	Women worried by the leaflet	
	Yes n (%)	No n (%)
Women who before receiving the leaflet:		
Had heard about spina bifida		
Yes	199 (23)	685 (77)
No	15 (32)	32 (68)
Had heard there was a screening test available for spina bifida		
Yes	140 (21)	542 (79)
No	74 (29)	175 (70)
The leaflet told the women:		
Nothing new	42 (17)	20 (83)
A few new things	94 (20)	366 (80)
Nearly all new information	77 (35)	142 (65)

Of those who did not know whether they would have a termination, 97% said they wanted to know as soon as possible if they were carrying a spina bifida baby. Although they were not able to say what they would do in such an instance, almost all preferred to be in the position of having to make that decision.

Anxiety associated with the leaflet

The women were asked if the the leaflet worried them at all. There was a positive association between never having heard of spina bifida and being worried by the leaflet ($\chi^2_1=8\cdot56$, $P<0\cdot01$) and between never having heard of a screening test and being worried by the leaflet ($\chi^2_1=8\cdot19$, $P<0\cdot01$) (Table 3).

There was a significant positive association between how much of the information given in the leaflet was new to the women and being worried by the leaflet ($\chi^2_2=65\cdot94$, $P<0\cdot001$).

Being worried by the leaflet was also positively associated with not having enough information to decide whether or not to accept the screening test ($\chi^2_1=25\cdot41$, $P<0\cdot001$) (Table 3).

Intentions and behaviour

Checking against AFP screening records allowed the woman's stated intentions to be compared with her actions. We were able to link 914 women with the test records (95·5% of the respondents) and 78·6% of these had the test. Of the 78% who said they intended to have the test, 86% did so, but 13% did not. Of the women who had not made up their minds 70% went on to have the test, while 60% of those who had said they needed more information before deciding to accept the test subsequently had it. Only two women who had said that they definitely did not want the test eventually had it.

We did not have the names of non-responders to the questionnaire. Since we recruited the sample according to booking dates, not dates of AFP testing, it was not possible to link them one-to-one with test records. We do know that of

5160 who booked in 1984, 75·8% accepted the AFP test. The booking figure includes a small number of late bookers to whom it was not possible to offer the test and who were not sent a leaflet. Allowing for late bookers, the percentage of responders accepting the AFP test is very similar to the overall acceptance rate for 1984. It remains possible that non-responders had a different uptake to responders and to 1984 bookers as a whole. If so, the overall AFP acceptance rate for the first quarter of 1984 would have been very different from the overall acceptance rate for the rest of the year. This seems unlikely, and we conclude that the test acceptance rate of non-responders was broadly similar to that of responders.

Discussion

Our survey found no evidence that patients' resistance to serum AFP screening contributed to low uptake. Nearly all the women who replied thought screening was a good idea. This was a much higher proportion than said that they would definitely accept the test, implying that even those women who do not want the test themselves are not opposed to other people having it.

The linkage of the survey with test records indicated that most of the women who said they intended to have the test did go on to have it, as did most of those who had not made up their minds at the time of the survey. Clearly, therefore, some women need more time to come to a decision. Requiring instant decisions is likely to reduce the acceptability of the test, while staff counselling could increase the acceptance rate.

Having no prior knowledge of spina bifida or the screening was significantly associated with anxiety on receiving the leaflet. New discovery of a risk to the baby in early pregnancy seems to cause more anxiety than the same information given to pregnant women who are already aware of the possibility. To ensure women are not unduly worried by the AFP screening test, it seems that either they should be given no information about it, which is neither ethically acceptable nor practical, or that information should be widely available, preferably before pregnancy. Other workers have reported less maternal anxiety in areas with access to AFP screening programmes than in areas without them, but have concentrated on mid to late pregnancy (Burton *et al.* 1985*a*; Berne-Fromell & Kjessler 1984) or on women with high levels of serum AFP (Fearn *et al.* 1982; Burton *et al.* 1985*b*). A consensus meeting about maternal serum AFP screening held in Berlin in 1983 concluded that 'sufficient information and counselling help to relieve anxiety and should be provided at an early stage in any large scale screening programme' (Anon 1985). Our results confirm this.

Although most women had already heard of spina bifida and the existence of a test, many had not heard this from a medical source. Although the leaflet was primarily intended to complement and facilitate further medical discussion and counselling, it seemed in practice to fill an information gap. Experience with the South Wales programme, where general practitioners were asked to distribute an explanatory leaflet, indicated a reluctance by them to discuss neural tube defects in early pregnancy (Fearn *et al.* 1982). A leaflet such as the one used in this survey could act as a useful primer to the booking visit, because it invites discussion of the test. Leaflets have been shown to be useful in imparting knowledge in American screening programmes (Faden *et al.* 1985), although no leaflet can be a substitute for adequate patient–doctor discussion (Annas & Elias 1985).

The obstetrician's increased ability to identify pregnancies where all is not well should be made clear to all women, certainly as soon as possible after they become pregnant, if not before. Harris & Read (1981) were principally concerned with routine ultrasound screening when they stated that informed consent should always be obtained before screening for neural tube defects, but this is equally true for serum AFP or any other screening tests which might lead to the offer of termination, for example HIV screening. It is not acceptable to hide behind a battery of tests described as 'just routine', until a suspicious result occurs. The natural anxiety of being in a high-risk group is not only likely to be much greater if this is the first time that the woman realizes the potential significance of such 'routine tests', but is also likely to prevent the information presented from being absorbed.

It might be tempting to measure demand for an antenatal screening service in terms of the numbers of patients who are prepared to commit themselves to the termination of their pregnancies if the final result is positive. This study suggests otherwise. Many women did not know whether they would accept termination if they were carrying a fetus with spina bifida; nevertheless, they wanted to know this as soon as possible in their pregnancies.

The screening service at the Birmingham Maternity Hospital works on the 'opt-in' principle, i.e. women specifically elect to have the test. The consensus meeting in 1983 did not agree whether screening should be on an 'opt-in' or 'opt-out' basis. Since then, serum AFP has increased in usefulness as a biochemical indicator of pregnancy risk, for example as a predictor of low birthweight (Wald *et al.* 1982). As the test becomes more useful in clinical practice, there will be pressure for it to be measured routinely in all pregnancies whether or not an individual's consent to be screened for neural tube defects has been obtained. This does not absolve doctors from explaining the possible consequences to the patient at the outset.

Ethically, an 'opt-out' system might be desirable. The worst outcome of an 'opt-out' system, if administrative error causes the test to be done on a woman who 'opted-out', is a burden that hospital staff must bear of knowing a woman has a high serum AFP level but ignoring it as she had chosen to 'opt-out'. In an 'opt-in' system, the worst possible outcome is where a woman wants the test, but for some reason fails to 'opt-in' and goes on to have a child with a neural tube defect.

The widespread acceptance of the principle of screening in our survey indicates that an 'opt-out' system with adequate explanation of the test and real opportunities for opting out is likely to be acceptable. As we have found no evidence that the attitudes of patients have any significant effect on uptake of serum AFP screening, we believe that changing to 'opt-out' systems of testing is likely to increase the proportion of women tested.

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References

Annas, G J. & Elias, S. (1985) Maternal serum AFP· educating physicians and the public. *Am J Public Health* **75**, 1374-1375.

Anon (1985) Maternal serum alpha-fetoprotein screening for neural tube defects: results of a consensus meeting. *Prenatal Diagn* **5**, 77-83.

Berne-Fromell, K. & Kjessler, B. (1984) Anxiety concerning fetal malformations in pregnant women exposed or not exposed to an antenatal serum alpha-fetoprotein screening program. *Gynecol Obstet Invest* **17**, 36-39.

Burton, B. K , Dillard, R G. & Clark, E. N. (1985*a*) Maternal serum alpha-fetoprotein screening: the effect of participation on anxiety and attitude toward pregnancy in women with normal results. *Am J Obstet Gynecol* **152**, 540-543.

Burton, B. K., Dillard, R G. & Clark, E N. (1985*b*) The psychological impact of false positive elevations of maternal serum AFP *Am J Obstet Gynecol* **151**, 77-82

Faden, R. R., Chwalow, A. J., Orel-Crosby, E., Holtzman, N. A., Chase, G. A. & Leonard, C. O. (1985) What participants understand about a maternal alpha-fetoprotein screening program. *Am J Public Health* **75**, 1381-1384.

Fearn, J , Hubbard, B M., Laurence, K M., Roberts, A. & Robinson, J. O (1982) Screening for neural tube defect and maternal anxiety. *Br J Obstet Gynaecol* **89**, 218-221.

Harris, R & Read, A. P. (1981) New uncertainties in prenatal screening for neural tube defect. *Br Med J* **i**, 1416-1418.

Wald, N J., Cuckle, H. S., Boreham, J., Stirrat, G. M & Turnbull, A C. (1982) Maternal alpha-fetoprotein and low birthweight risk according to gestational age. *Br J Obstet Gynaecol* **89**, 216-217.

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Changes in postprandial release patterns of gastrointestinal hormones in late pregnancy and the early postpartum period

TROND G. JENSSEN, HANNE H. HAUKLAND, BARTHOLD VONEN,
JON FLORHOLMEN, PER G. BURHOL, JAN M. MALTAU

Summary. Intestinal transit time increases and gastrointestinal incretin effect is reported to decrease in pregnancy. The release patterns of gastrointestinal hormones related to these functions were studied in eight women before and after ingestion of a standardized meal at 32–34 weeks gestation and at 4 days postpartum. Basal plasma motilin and the integrated meal response of motilin, pancreatic polypeptide (PP) and gastric inhibitory polypeptide (GIP) were significantly lower in pregnancy than postpartum. The meal-induced rise of somatostatin and vasoactive intestinal polypeptide (VIP) was, however, absent in late pregnancy; whereas the somatostatin response recovered postpartum, and the plasma VIP concentrations stabilized at significantly higher levels postpartum without any meal response. Basal and meal-induced plasma insulin were significantly higher in pregnancy.

Pregnancy is associated with pronounced changes in gastroentero-pancreatic functions. First, the intestinal transit time is delayed in the second and third trimester (Hytten 1980; Lawson *et al.* 1985; Wald *et al.* 1982), and this inhibition of propulsion is combined with a general relaxation of the upper gastrointestinal sphincters (Hytten 1980).

These effects on the motor activity of the gastrointestinal tract have so far mainly been ascribed to the increasing levels of progesterone in late pregnancy (Wald *et al.* 1982; Lawson *et al* 1985), since progesterone both *in vitro* and *in vivo* relaxes alimentary smooth muscle (Bruce & Behsudi 1979; Shaffer *et al.* 1984). However, lately it has been shown that the gastrointestinal hormone motilin, which stimulates the propulsion waves of the antroduodenal area in the fasting state (Janssens *et al.* 1983), circulates in lower concentrations in late pregnancy than in the postpartum period (Christofides *et al.* 1982; Jenssen *et al.* 1986*b*). Several other gastrointestinal hormones, such as somatostatin, pancreatic polypeptide (PP) and vasoactive intestinal polypeptide (VIP) also have effects on smooth muscle contractility in digestive organs. Thus, somatostatin has recently been attributed a physiological role in the initiation of the migrating intestinal contractions of the duodenum and jejunum (Peeters *et al.* 1983). But knowledge of their release characteristics in pregnancy is still deficient.

Second, glucose tolerance decreases in pregnancy (Pedersen 1977). This may partly be

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Departments of Medicine (Laboratory of Gastroenterology) and Gynaecology and Obstetrics, University Hospital of Tromsø, N-9012 Tromsø, Norway
TROND G. JENSSEN
HANNE H. HAUKLAND
BARTHOLD VONEN
JON FLORHOLMEN
PER G. BURHOL
JAN M. MALTAU

Correspondence: Dr T G. Jenssen

explained by a state of insulin resistance (Burt & Davidson 1974). In addition, others (Hornnes *et al.* 1978) have reported that the physiological incretin effect of the gastrointestinal tract, which accentuates the postprandial insulin release, is reduced in pregnancy. This may possibly be ascribed to impaired release of the incretin hormone gastric inhibitory polypeptide (GIP) (Hornnes *et al.* 1979).

The present study was undertaken to assess the meal response of plasma motilin, somatostatin, PP, VIP, insulin and GIP in late pregnancy and after parturition.

Patients and methods

Eight healthy women, 20–31 years old, all primigravidae of gestational age 32–34 weeks, were studied after their informed consent was obtained. They were recruited among the outpatients of the Department of Obstetrics and Gynaecology, and all had uncomplicated pregnancies with normal weight gain. None of the patients received any medication during pregnancy or the early postpartum period.

At inclusion all patients were studied after an overnight fast. They consumed a 15-min standardized meal consisting of 150 g milk, 120 g bread, 18 g butter, 25 g jam, 75 g hamburger and 30 g ham salad (26 g protein, 46 g fat, 93 g carbohydrates). Blood samples were drawn from an indwelling catheter in an antecubital vein at 30, 15 and 0 min before, and at 10, 20, 30, 45, 60, 90, 120, 150 and 180 min after start of the meal. The protocol was then repeated 4 days postpartum.

Plasma motilin, somatostatin, PP, VIP, insulin and GIP were measured by radioimmunoassays described previously (Jenssen *et al.* 1984; Burhol *et al.* 1978, 1980, 1984; Jorde & Burhol 1982; Jorde *et al.* 1981). Blood glucose was measured by a hexokinase method (Glucoquant, Boehringer Mannheim, FRG).

Postprandial responses were assessed by comparing the integrated 30-min basal plasma levels with the integrated plasma levels in 30-min periods postprandially. Furthermore, the integrated basal levels before and after parturition were compared, as well as the total integrated postprandial responses at the same occasions taking fasting values as baseline. A paired Wilcoxon rank sum test was used for comparisons. Where no meal response was observed, the overall hormone concentrations before and after parturition were compared by analysis of variance. $P<0{\cdot}05$ was each time considered statistically significant, and all results were presented as mean ± standard error of the mean (SEM) values.

Results

Motilin. During the first 30-min postprandial period plasma motilin rose significantly both in pregnancy and postpartum, but the basal levels as well as the integrated meal response were significantly lower in pregnancy (Fig. 1).

Somatostatin. Basal levels of somatostatin pre- and postpartum did not differ whereas a postprandial rise in plasma somatostatin could only be detected after delivery, reaching statistical significance for the last 2 h of the study (Fig. 1).

PP. Basal plasma PP concentrations were the same before and after delivery, rose significantly for the whole postprandial period on both occasions, but the meal response in pregnancy was clearly reduced ($P<0{\cdot}05$) (Fig. 1).

VIP. No meal response was observed either in pregnancy or postpartum, but the overall plasma VIP levels were significantly higher postpartum (Fig. 1).

Insulin. A significant postprandial rise was observed both before and after delivery, whereas the basal plasma insulin levels as well as the integrated postprandial plasma levels were significantly higher in pregnancy (Fig. 2).

GIP. Although basal plasma GIP concentrations did not differ, the meal response of GIP was significantly reduced in pregnancy (Fig. 2).

Blood glucose. Basal blood glucose levels did not differ between the pre- and postpartum periods, but the integrated postprandial rise in blood glucose was significantly accentuated in pregnancy (Fig. 2).

Discussion

In accordance with previous reports (Christofides *et al.* 1982; Hornnes *et al.* 1979, 1981*a*; Hornnes & Kühl 1981*a*; Jenssen *et al.* 1986*b*), this study shows that the release pattern of several gastrointestinal hormones is altered in

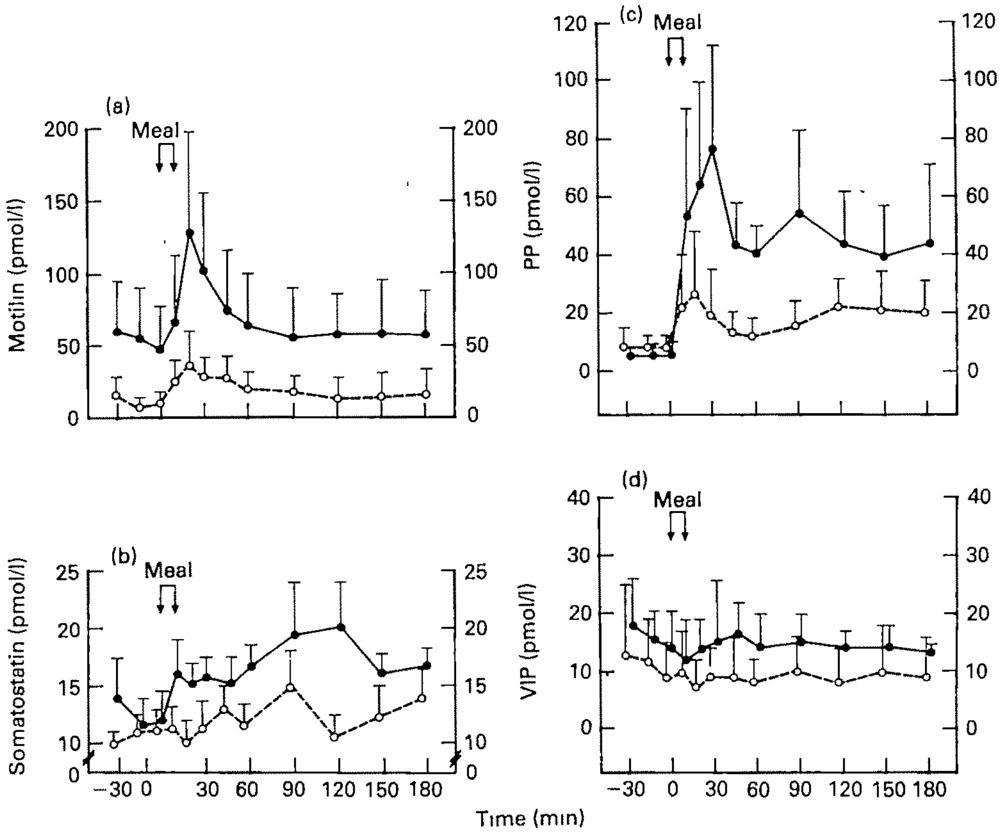

Fig. 1. Pre- and postprandial plasma concentrations of motilin (a), somatostatin (b), pancreatic polypeptide (PP) (c) and vasoactive intestinal polypeptide (VIP) (d) in eight women before (○——○) and after (●——●) parturition. Each point represents the mean of eight observations, and the vertical bars the standard errors of the means.

pregnancy. Most striking is that the ordinary meal response of plasma somatostatin seems to be missing in late pregnancy. One group (Peeters *et al.* 1983) has demonstrated that somatostatin probably plays a physiological role in the induction of migrating contractions in the upper intestines between meals, and somatostatin probably has a similar effect in the postprandial state (Sarna *et al.* 1984). Other important aspects of this hormone are its inhibition of the secretion of acid from the stomach (Bloom *et al.* 1974), alcalic juice from the pancreas (Hanssen *et al.* 1977) and the release of several gastrointestinal hormones (Colturi *et al.* 1984; Jenssen *et al.* 1986*a*). Future work may reveal a role for somatostatin in the regulation of these functions in pregnancy.

As previously reported, both basal (Christofides *et al.* 1982; Jenssen *et al.* 1986*b*) and postprandial (Christofides *et al.* 1982) levels of motilin are lower in pregnancy than postpartum. Motilin is spontaneously released during initiation of the antroduodenal contractions in the fasting state (Vantrappen *et al.* 1979), and when administered intravenously it is also able to induce an identical motor response (Janssens *et al.* 1983). The rate of gastric emptying is both reported to be normal (Hunt & Murray 1958) and reduced (Davison *et al.* 1970) in pregnancy, whereas the intestinal transit time is delayed during the second and third trimester (Hytten 1980; Lawson *et al.* 1985; Wald *et al.* 1982). The reduced motilin release in late pregnancy may either reflect impaired intestinal propulsion in the fasting state, or, more interestingly, it may be responsible for the reduced intestinal motility of late pregnancy.

The impairment of postprandial PP release in pregnancy is in accordance with the findings of Hornnes & Kühl (1981) that the ordinary meal

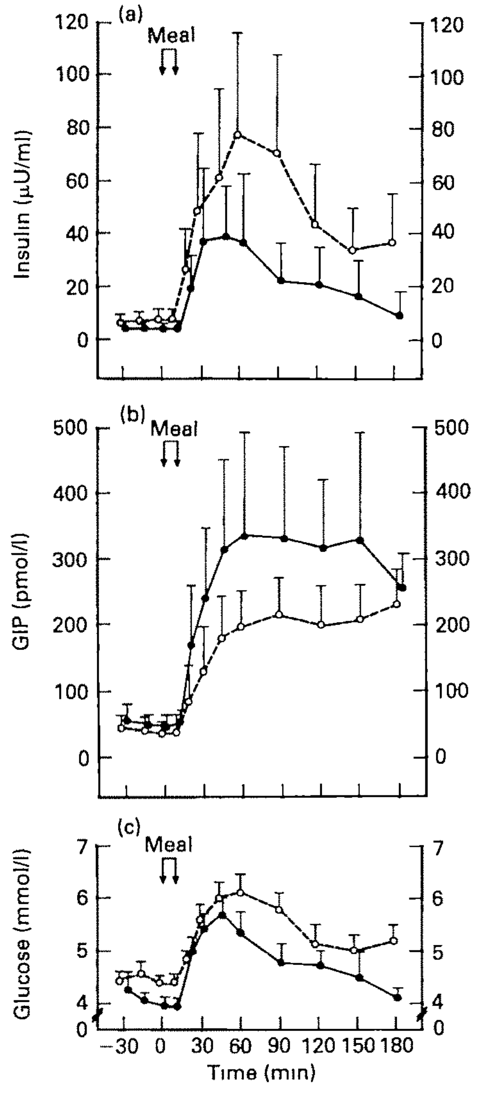

Fig. 2. Pre- and postprandial concentrations of plasma insulin (a), gastric inhibitory polypeptide (GIP) (b) and blood glucose (c) in eight women before (O——O) and after (●——●) parturition. Each point represents the mean of eight observations, and the vertical bars the standard errors of the means.

response of PP had recovered 6–20 weeks postpartum. Our study shows that this release pattern probably is restored within a few days after delivery. PP is released from the pancreas during antroduodenal contractions in the fasting state (Janssens *et al.* 1982), and the level of its release depends upon the vagal cholinergic tone (Schwartz 1983). Thus, the reduced release of PP may not only describe the impairment of intestinal motility in late pregnancy, but also a decreased cholinergic tone.

Furthermore, the circulating VIP concentrations usually increase during the second and third hour after a meal (Burhol *et al.* 1979). The present study does not show any postprandial VIP response either in pregnancy or in the early postpartum period, although the overall VIP levels apparently increase during the first days postpartum. It is generally believed that VIP serves as a neurotransmitter of the noncholinergic non-adrenergic autonomous nerve system (Sundler *et al.* 1980), and the VIP concentrations detected in the circulation are considered to represent an 'overflow' from the nerve synapses. The present findings therefore suggest that the general tone of this peptidergic nerve system is reduced in pregnancy, but possible physiological implications must await further studies.

The increased basal and postprandial insulin levels in pregnancy are in accord with previous reports (Hornnes *et al.* 1981*b*). Under physiological conditions insulin release is modulated by the inhibitory action of somatostatin (Colturi *et al.* 1984), and it is therefore also feasible that the enhanced postprandial insulin response is facilitated by the absence of postprandial somatostatin release. Nevertheless, the postprandial incretin effect is reported to be reduced by some 35% in pregnancy (Hornnes *et al.* 1978). The design of our study does not allow any firm conclusions in this respect, but it is of interest to note that the integrated postprandial GIP response in our study was reduced by some 37% in late pregnancy. GIP is the only gastrointestinal hormone so far shown to exert physiological incretin effects (Dupre *et al.* 1973), and the present findings lend further support to the notion that the postprandial insulin response in pregnancy is insufficient because of impaired GIP release from the gastrointestinal tract (Hornnes *et al.* 1979).

In conclusion, the fasting plasma motilin concentrations together with the postprandial concentrations of motilin, PP and GIP are lower in the third trimester than in the first days postpartum, whereas the postprandial responses of somatostatin and VIP seem abolished in late pregnancy. The meal response of somatostatin recovers during the first days postpartum, but not that of VIP although the overall circulating VIP levels increase. Both fasting and postprandial insulin levels are increased in the third trimester. This demonstrates that some of the metabolic changes taking place in pregnancy may be mediated by changes in the gastrointestinal endocrine system.

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References

Bloom, S. R., Mortimer, C. H., Thorner, M. O., Besser, G. M., Hall, R., Gomez-Pan, A., Roy, V. M., Russell, R. C. G., Coy, D. H., Kastin, A. J. & Schally, A. V. (1974) Inhibition of gastrin and gastric-acid secretion by growth-hormone release inhibiting hormone. *Lancet* **ii**, 1106-1109.

Bruce, L. A & Behsudi, F. M. (1979) Progesterone effects on three regional gastrointestinal tissues. *Life Sci* **25**, 729-734.

Burhol, P. G., Lygren, I. & Waldum, H. L. (1978) Radioimmunoassay of vasoactive intestinal polypeptide in plasma. *Scand J Gastroenterol* **13**, 807-813.

Burhol, P. G., Waldum, H. L., Jorde, R. & Lygren, I. (1979) The effect of a test meal on plasma vasoactive intestinal polypeptide (VIP), gastric inhibitory polypeptide (GIP), and secretin in man. *Scand J Gastroenterol* **14**, 939-943.

Burhol, P. G., Jorde, R. & Waldum, H. L. (1980) Radioimmunoassay of plasma gastric inhibitory polypeptide (GIP), release of GIP after a test meal and duodenal infusion of bile, and immunoreactive plasma GIP components in man. *Digestion* **20**, 336-345.

Burhol, P. G., Lygren, I., Jenssen, T. G., Florholmen, J. & Jorde, R. (1984) Somatostatin release and plasma molecular somatostatin components in man. *Acta Physiol Scand* **121**, 223-228.

Burt, R. L. & Davidson, I. W. F. (1974) Insulin half-life and utilization in normal pregnancy. *Obstet Gynecol* **43**, 161-170.

Christofides, N. D., Ghatei, M. A , Bloom, S. R., Borberg, C. & Gillmer, M. D. G (1982) Decreased plasma motilin concentrations in pregnancy. *Br Med J* **285**, 1453-1454.

Colturi, T. J., Unger, R. H. & Feldman, M. (1984) Role of circulating somatostatin in regulation of gastric acid secretion, gastrin release, and islet cell function. *J Clin Invest* **74**, 417-423.

Davison, J. S., Davison, M. C. & Hay, D. M. (1970) Gastric emptying time in late pregnancy and labour. *J Obstet Gynaecol Br Commonw* **77**, 37-41.

Dupre, J., Ross, S. A., Watson, D. & Brown, J. C. (1973) Stimulation of insulin secretion by gastric inhibitory polypeptide in man. *J Clin Endocrinol Metab* **37**, 826-828.

Hanssen, L. E., Hanssen, K. F. & Myren, J. (1977) Inhibition of secretin release and pancreatic bicarbonate secretion by somatostatin infusion in man. *Scand J Gastroenterol* **12**, 391-394.

Hornnes, P., Kühl, C & Klebe, J. G. (1978) Diminished gastrointestinal potentiation of insulin secretion in human pregnancy. *Diabetologia* **15**, 165-168.

Hornnes, P. J., Kühl, C. & Lauritsen, K B. (1979) Diminished gastric inhibitory polypeptide response to oral glucose in late human pregnancy. *J Clin Endocrinol Metab* **48**, 506-508.

Hornnes, P. J. & Kühl, C. (1981) Decreased plasma pancreatic polypeptide levels in pregnancy. *J Clin Endocrinol Metab* **52**, 605-607.

Hornnes, P. J., Kuhl, C. & Lauritsen, K. B. (1981*a*) Gastro-entero-pancreatic hormones in normal pregnancy: response to a protein-rich meal. *Eur J Clin Invest* **11**, 345-349.

Hornnes, P. J., Kuhl, C. & Lauritsen, K. B. (1981*b*) Gastrointestinal insulinotropic hormones in normal and gestational-diabetic pregnancy. Response to oral glucose. *Diabetes* **30**, 504-509.

Hunt, J. N. & Murray, F. A. (1958) Gastric function in pregnancy. *J Obstet Gynaecol Br Commonw* **65**, 78-83.

Hytten, F. (1980) The alimentary system In *Clinical Physiology in Obstetrics* (Hytten, F. & Chamberlain, G., eds), Blackwell Scientific Publications, Oxford, pp. 147-162.

Janssens, J., Hellemans, J., Adrian, T. E., Bloom, S R., Peeters, T. L., Christofides, N. & Vantrappen, G R. (1982) Pancreatic polypeptide is not involved in the regulation of the migrating motor complex in man. *Regul Pept* **3**, 41-49.

Janssens, J., Vantrappen, G. & Peeters, T. L. (1983) The activity front of the migrating motor complex of the human stomach but not of the small intestine is motilin-dependent. *Regul Pept* **6**, 363-369.

Jenssen, T. G., Burhol, P. G., Jorde, R., Florholmen, J. & Lygren, I (1984) Radioimmunoassayable plasma motilin in man Secretagogues, insulin-induced suppression, renal removal, and plasma components. *Scand J Gastroenterol* **19**, 717-723.

Jenssen, T. G., Haukland, H. H , Florholmen, J., Jorde, R. & Burhol, P. G. (1986*a*) Evidence of somatostatin as a humoral modulator of motilin release in man. *Scand J Gastroenterol* **21**, 273-280.

Jenssen, T. G., Holst, N., Burhol, P. G., Jorde, R., Maltau, J. M. & Vonen, B. (1986*b*) Plasma concentrations of motilin, somatostatin and pancreatic polypeptide before, during and after parturition. *Acta Obstet Gynecol Scand* **65,** 153-156.

Jorde, R., Burhol, P. G. & Waldum, H. L. (1981) The effect of a test meal on plasma gastric inhibitory polypeptide and serum gastrin in patients with achlorhydria and hypergastrinemia, and in patients with normal gastric H+ secretion *Digestion* **21,** 304-309.

Jorde, R. & Burhol, P. G. (1982) Duodenal acid is without importance for the postprandial PP release. *Scand J Gastroenterol* **17,** 681-685.

Lawson, M. L., Kern, F. & Everson, G. T. (1985) Gastrointestinal transit time in human pregnancy: Prolongation in the second and third trimesters followed by postpartum normalization. *Gastroenterology* **89,** 996-999.

Pedersen, J. (1977) *The Pregnant Diabetic and her Newborn.* Williams & Wilkins, Baltimore.

Peeters, T. L., Janssens, J. & Vantrappen, G. R. (1983) Somatostatin and the interdigestive migrating motor complex in man. *Regul Pept* **5,** 209-217.

Sarna, S. K., Garthwaite, T. L., Telford, G L. & Lang, I. M. (1984) Somatostatin prevents the disruption of MMC by feeding. *Gastroenterology* **86,** 1232.

Schwartz, T. W. (1983) Pancreatic polypeptide: A hormone under vagal control. *Gastroenterology* **85,** 1411-1425.

Shaffer, E. A., Taylor, P. J., Logan, K., Gadomski, S. & Corenblum, B. (1984) The effect of a progesterin on gallbladder function in young women. *Am J Obstet Gynecol* **148,** 504-507.

Sundler, F., Håkanson, R. & Leander, S. (1980) Peptidergic nervous systems in the gut. *Clin Gastroenterol* **9,** 517-543

Vantrappen, G., Janssens, J., Peeters, T. L., Bloom, S. R., Christofides, N. D. & Hellemans, J. (1979) Motilin and the interdigestive migrating motor complex in man. *Dig Dis Sci* **24,** 497-500.

Wald, A., Van Thiel, D. H., Hoechstetter, L., Gavaler, J. S., Egler, K. M., Verm, R., Scott, L. & Lester, R. (1982) Effect of pregnancy on gastrointestinal transit. *Dig Dis Sci* **27,** 1015-1018.

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Daily variability of umbilical and lateral uterine wall artery blood velocity waveform measurements

STEWART J. HASTIE, CATHERINE A. HOWIE,
MARTIN J. WHITTLE, PETER C. RUBIN

Summary. The daily variability of umbilical artery and lateral uterine wall artery velocity-time waveforms recorded by continuous wave Doppler ultrasound was determined by making three observations in each of 97 women on different days within a 7-day period. There were no significant changes in the maximal:minimal Doppler shift frequency (A/B ratio) or the pulsatility index in either artery over the period of study. Common pregnancy complications did not influence the variability of the recordings. The variability of uterine artery recordings was not affected by gestational age between 17 and 41 weeks but the degree of variability of the umbilical artery recordings was greater before 30 weeks. We conclude that after 30 weeks gestation this technique has an acceptable range of daily variability for clinical and research applications.

Fetal and uteroplacental blood flow evaluation using Doppler ultrasound has recently attracted considerable research interest because of the technique's simplicity, apparent safety and possible clinical application. An important factor in determining the usefulness of these measurements will be the reproducibility of the technique used.

In vitro, pulsed wave Doppler ultrasonic evaluation of blood volume flow and velocity is highly accurate (Gill 1980; Erskine & Ritchie 1985), but *in vivo* a number of methodological problems limit the accuracy. These errors relate to difficulties in the accurate measurements of both the Doppler beam angle of insonation and the blood vessel diameter (Gill 1980; Gill *et al.* 1981; Griffin *et al.* 1983; Eik-nes *et al.* 1984; Erskine & Ritchie 1985). Interest has therefore evolved in blood velocity waveform analysis, an indirect assessment of blood flow and downstream impedance to flow. These waveforms may be recorded with the simpler continuous wave Doppler ultrasound because display of the vessel being studied, that pulsed Doppler demands, is not necessary. Trudinger *et al.* (1985) validated continuous wave Doppler recordings of both umbilical and maternal uterine artery waveforms by use of a combined Doppler B-mode system which allowed precise location of the sample volume for Doppler recording on a B-mode image.

The variability of blood velocity waveform measurements in the same woman on different days is of practical importance and has not been examined previously. The current study addresses this question for both the umbilical artery and the maternal lateral uterine wall

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Departments of Midwifery and Materia Medica, University of Glasgow, Queen Mother's Hospital, Glasgow
STEWART J. HASTIE *Wellcome Trust Research Fellow*
CATHERINE A. HOWIE *Research Assistant*
MARTIN J. WHITTLE *Consultant Obstetrician*
PETER C. RUBIN *Wellcome Trust Senior Fellow in Clinical Science*

Correspondence: Professor P. C. Rubin, Department of Therapeutics, University Hospital, Nottingham NG7 2UH

artery blood velocity waveforms. Variability has been assessed in normal pregnancies, in a number of common pregnancy complications and also at different gestational ages.

Patients and methods

The study was approved by the hospital ethics committee and all patients gave informed consent. The 100 women who completed the study were recruited from the antenatal clinics and wards. The only criterion used for inclusion of women in the study was that they were available for the three separate days measurements within a 7-day period. This inevitably resulted in a larger proportion of the women being well advanced in pregnancy.

Blood velocity waveforms were recorded using an Appleton Angioscan III (Unigon-Ultrasonix, New York) with a 4 MHz ultrasound frequency continuous wave probe having a transmitted beam power density of 6·5 mW/cm (Technical Report, Unigon-Ultrasonix). The spectrum analyser used a fast Fourier method of analysis and the waveform produced was displayed on a monitor and hard-copied. Recordings were made with the woman resting in a semirecumbent position to avoid supine hypotension. Each subject's blood pressure was recorded before and during each session to ensure that hypotension did not occur. A real-time ultrasound scanner was used to identify the umbilical cord and the Doppler beam was then directed towards the cord to record the umbilical artery waveforms which were recognized by their characteristic appearance. No attempt was made to display the lateral uterine wall artery. The Doppler recording of this artery was made by directing the Doppler probe superiorly and medially towards the lateral uterine wall from one or the other of the subject's iliac fossae, approximately 3 to 5 cm above the inguinal ligament. Again this vessel's waveform was recognized by its characteristic appearance. The position of the placenta was not considered in this study.

Irregular waveforms arising as a result of fetal or maternal movement were not used for analysis. Once regular waveforms were recorded the image was frozen. A screen time of 1·6 s allowed either four or five umbilical artery waveforms or two to three uterine wall artery waveforms to be displayed and analysed. The electronic calipers were employed to measure the maximal (A) and the minimum (B) Doppler shift frequency. The mean Doppler shift frequency was calculated by the microcomputer within the apparatus as a mean over time of the complete waveforms displayed upon the screen. The A/B ratio and the pulsatility index (PI) calculated as (A−B)/mean Doppler shift frequency, were then derived.

These recordings were repeated for each subject on three separate days over a period of no more than 7 days by a single observer (S.J.H.). Women in whom complete sets of recordings from each artery were not possible within the 7-day time span were excluded from the study. This was a small group who were usually obese or were not available to complete the study for unrelated reasons. All 100 women who completed the study had no significant change in their clinical condition during the study period. There were three women who had on at least 1 day apparently zero end-diastolic velocities (B fell below the instrument's low frequency filter of 300 Hz) in the umbilical artery, invalidating the use of the A/B ratio. The measurements from these three women were not used for analysis.

Statistical analysis

Data are presented as mean (SD). Day to day variability and the possible effect on daily variability of gestational age and pregnancy complications were examined using Levene's test of homogeneity of variance and repeated measures analysis of variance. Recordings were made within three gestational age groups: 17–30 weeks, 31–36 weeks and 37–41 weeks. A group of women with normal pregnancies was studied, as were groups of subjects with the following disorders: hypertension, antepartum haemorrhage, and a group with a number of miscellaneous pregnancy complications.

Results

The measurements from 97 subjects in whom complete sets of measurements were made within the 7-day interval were used for analysis. The age of the subjects was 26·6 (5·8) years and the gestation at the time of the first test ranged from 17 to 41 weeks. In 51 women the pregnancy was complicated at the time of the study and in 46 the pregnancy was normal.

The mean (SD) individual daily umbilical artery A/B ratios were 2·67 (0·68), 2·66 (0·73) and 2·65 (0·65) respectively, and pulsatility indices were 0·99 (0·18), 1·0 (0·17) and 1·00 (0·17). The mean daily uterine wall artery indices were: A/B ratios 1·87 (0·28), 1·84 (0·27) and 1·84 (0·26) and pulsatility indices 0·81 (0·16), 0·78 (0·16) and 0·79 (0·15) respectively. There was no statistically significant difference in daily variance in any of the waveform indices over the days of study (*P*>0·05, Table 1).

Variability was significantly influenced by gestational age at testing in indices of the umbilical artery waveform, but not in the lateral uterine artery waveform indices (Table 2). Variability was not, however, influenced in either artery by the pregnancy complications studied (Table 3).

Discussion

This study demonstrates the daily variability of two blood velocity waveform indices recorded from the fetal umbilical artery and the maternal uterine wall artery. The degree of variability was not statistically significant.

Daily variability of umbilical artery and uterine artery blood velocity waveforms has not been previously reported, although such data are of considerable importance if the technique is to be introduced into clinical practice. In agreement with other published data, we found that the degree of variability in these waveform indices from day to day within a period of 7 days was not statistically significant in pregnancies with a stable clinical condition. Schulman *et al.* (1984) reported an average error of 6% in 80 randomly selected umbilical artery A/B ratio readings in 20 women at different gestational ages. FitzGerald *et al.* (1984), examining the same artery but analysing the PI and another waveform index, the angle of acceleration, found 'no significant differences' in recordings taken from 17 subjects within 30–60 min. Murrills *et al.* (1986) reported up to 12·1% inter-observer variation and up to 10·9% intra-observer variation for a single subject in the umbilical artery.

The significant change with gestation in variability of the umbilical artery waveform indices occurred because the variance in the earliest group (17–30 weeks) was greatest. Thus, the observation of large variation in measurements before 30 weeks may be of no clinical significance. It is unclear why this greater variability occurs in the second trimester but, speculatively,

Table 1. Blood velocity indices mean (SD). trend with time

Waveform index	Day 1	Day 2	Day 3	*P* value
n	97	97	97	
Umbilical artery				
A/B ratio	2·67 (0·68)	2·66 (0·73)	2·65 (0·65)	0·88
PI	0·99 (0·18)	1·0 (0·17)	1·0 (0·17)	0·88
Uterine wall artery				
A/B ratio	1·87 (0·28)	1·84 (0·27)	1·84 (0·26)	0·87
PI	0·81 (0·16)	0 78 (0·16)	0·79 (0·15)	0·41

Data analysed by repeated measures of analysis of variance.

Table 2. Blood velocity waveform indices standard deviations. influence of gestational age at testing

	Gestational age (weeks)			
Waveform index	17–30	31–36	37–41	*P* value
n	18	39	40	
Umbilical artery				
A/B ratio	0·93	0·53	0 42	0·02
PI	0·14	0·17	0·16	0·86
Uterine wall artery				
A/B ratio	0·25	0 26	0·30	0·99
PI	0·13	0·15	0·16	0·26

Data analysed by Levene's test for equal variance using first day measurements

Table 3. Blood velocity waveform indices standard deviations: influence of pregnancy complications

Waveform index	Hypertension	APH	Miscellaneous	Normal	*P* value
n	27	17	7	46	
Umbilical artery					
A/B ratio	0·95	0·58	0·58	0·54	0·30
PI	0·21	0·19	0·21	0·15	0·23
Uterine wall artery					
A/B ratio	0·26	0·24	0·34	0·29	0·73
PI	0·16	0·12	0·21	0·16	0·39

APH, Antepartum haemorrhage.
Data analysed by Levene's test for equal variance using first day measurements.

it may represent some instability of the fetoplacental vasculature at this time.

Of vital importance in terms of the clinical potential of the technique is the fact that after 30 weeks gestation the daily variability of the umbilical and uterine wall artery measurements was not significant regardless of whether or not the pregnancy was complicated. This implies that after 30 weeks gestation any consistent trend in waveform indices over at least 7 days is likely to reflect a genuine change in the fetoplacental or uteroplacental circulation that may be of clinical significance.

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References

Eik-nes, S. H., Marsal, K. & Kristoffersen, K. (1984) Methodology and basic problems related to blood flow studies in the human fetus. *Ultrasound Med Biol* **10,** 329-337

Erskine, R. L. A. & Ritchie, J. W. K (1985) Quantitative measurement of fetal blood flow using Doppler ultrasound. *Br J Obstet Gynaecol* **92,** 600-604.

FitzGerald, D. E., Stuart, B., Drumm, J. E. & Duigan, N. M. (1984) The assessment of the fetoplacental circulation with continuous Doppler ultrasound. *Ultrasound Med Biol* **10,** 371-376.

Gill, R. W. (1980) Fetal blood flow. In *Recent Advances in Perinatology, Pathology and Physiology* (White, D. N., ed.), Research Studies Press, John Wiley & Sons Ltd, Chichester, pp. 161-174.

Gill, R. W., Trudinger, B. J., Garrett, W. J , Kossoff, G. & Warren, P. S. (1981) Fetal umbilical venous flow measurement *in utero* by pulsed Doppler and B-mode ultrasound. 1. Normal pregnancies. *Am J Obstet Gynecol* **139,** 720-725.

Griffin, D., Cohen-Overbeek, T. & Campbell, S. (1983) Fetal and uteroplacental blood flow. *Clin Obstet Gynaecol* **10,** 565-602

Murrills, A. J., Gorman, F., Bamford, P. N , Gazzard, V. M. & Keen, A. C. (1986) Reproducibility in umbilical artery blood velocity waveforms. *Abstract Book of Obstetric & Neonatal Blood Flow Meeting, Biological Engineering Society,* London.

Schulman, H , Fleischer, A., Stern, W., Farmakides, G., Jagani, N. & Blattner, P. (1984) Umbilical velocity wave ratios in human pregnancy. *Am J Obstet Gynecol* **148,** 985-990

Trudinger, B. J., Giles, W. B. & Cook, C. M. (1985) Flow velocity waveforms in the maternal uteroplacental and fetal umbilical circulations. *Am J Obstet Gynecol* **152,** 155-160.

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Doppler assessment of the cardiac and uteroplacental circulations in normal and complicated pregnancies

W. AL-GHAZALI, M. G. CHAPMAN, L. D. ALLAN

Summary. Blood flow velocity waveforms were recorded in four sites in the fetal circulation in a series of 271 normal and 71 complicated pregnancies. The sites were the umbilical artery, the uterine artery branches in the placental bed, and distal to the two arterial valves in the heart. The blood flow through the arterial valves was added to estimate combined cardiac output. Normal ranges for values in all sites were established in our own series, and were similar to other published results. Abnormality of the waveform in the umbilical artery proved the most useful predictor of perinatal morbidity. Reversal of the normal pattern of increasing diastolic flow in the umbilical artery with advancing gestation was an important prognostic finding in the pregnancies studied serially. The combined cardiac output did not fall until late in the course of fetal compromise, and low values were seen only with an abnormal umbilical artery tracing.

Recent advances in Doppler ultrasound technology have permitted the assessment of the intact human fetal circulation throughout gestation. Fitzgerald & Drumm (1977) and McCallum *et al.* (1978) recorded blood flow velocity waveforms from the arteries of the umbilical cord using pulsed or continuous wave Doppler with velocity frequency spectrum analysis. Changing waveforms have been recorded during pregnancy, reflecting the decrease in placental resistance that occurs as pregnancy advances (Trudinger & Cook 1982; Schulman *et al.* 1984; Fitzgerald *et al.* 1984). These waveforms have been studied in abnormal pregnancy by Trudinger & Cook (1982), Trudinger *et al.* (1985*a*) and Giles *et al.* (1985) and show a relative decrease in diastolic flow in growth-retarded fetuses. Uterine artery flow velocity waveforms have been studied in normal and high-risk pregnancies. There is decreased diastolic flow in this site in hypertensive patients and in some cases of growth failure (Campbell *et al.* 1983; Trudinger *et al.* 1985*b*).

The volume of blood flow in the fetus has been estimated from the umbilical vein and descending aortic traces (Eik-Nes *et al.* 1980, 1982; Gill *et al.* 1981; Kirkinen *et al.* 1983). A decrease in volume blood flow estimated from the umbilical vein was reported in association with intrauterine growth retardation (Jouppila & Kirkinen 1984). There have been some recent publications on the direct measurement of cardiac output in the heart in normal pregnancy (Reed *et al.* 1986; Allan 1986; Allan *et al.* 1987) but to our knowledge no previous reports of cardiac output at these sites in complicated pregnancy.

In this study we examined the flow velocity waveforms in the placental bed and the umbilical artery and the combined cardiac output from

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Guy's Hospital, London SE1 9RT
Department of Perinatal Cardiology
W. AL-GHAZALI
L. D. ALLAN

Department of Obstetrics
M. G. CHAPMAN

Correspondence. W. Al-Ghazali

both sides of the fetal heart both in normal and complicated pregnancies.

Patients and methods

A series of 300 normal pregnant patients were recruited from the antenatal clinic or from referrals to our unit for fetal echocardiography. In all patients gestational age had been established by ultrasound in the early second trimester, and ranged from 16 to 42 weeks. A further 71 patients with complications of pregnancy were collected for study from the antenatal wards. These patients included 39 with pregnancy-induced hypertension, of whom five also had essential or renal hypertension, 25 with suspected intrauterine growth retardation and seven with both. Pregnancy-induced hypertension was defined as proteinuric hypertension where the diastolic pressure exceeded 95 mmHg. Suspected intrauterine growth retardation was defined as clinical discrepancy of >2 weeks combined with an abdominal circumference below the 10th centile on ultrasound measurement (Campbell 1976). The abnormal pregnancies were studied serially every 1–2 weeks until delivery.

Doppler assessment of each fetus, using a Hewlett-Packard 77020A phased array sector scanner, was made at the following four sites: the ascending aorta, the pulmonary artery, the umbilical cord and the uteroplacental bed. The methods of examination of each site have been described previously (Allan *et al.* 1987; Al-Ghazali *et al.* 1987). The cardiac output was calculated from the flows through each great artery from the formula:

Output in ml/min = (angle corrected) mean velocity × vessel area.

In postnatal life the ventricles function in series and have exactly the same output. In contrast, in fetal life the two ventricles function in parallel and have different outputs. Thus, the flows through each great artery must be added together to provide an estimate of combined cardiac output.

The systolic/diastolic (A/B ratio) of the arterial waveform was calculated from the umbilical cord tracing. The diastolic/systolic ratio of velocities in the uterine vessel traces was estimated as a percentage.

Results

Of the 300 pregnancies presumed normal, 29 developed complications at a later date Therefore the data used as the normal base were derived from 271 pregnancies which had a normal outcome at subsequent follow-up. The normal range for fetal combined cardiac output was established and ranged from about 100 ml/min at 16 weeks to 1200 ml/min at 40 weeks gestation. In our series, the normal range for the A/B ratio in the umbilical artery decreased as pregnancy advanced, from 4·5 (SD 2) at 16 weeks to 2·2 (SD 0·5) at 42 weeks (Fig. 1). The diastolic/systolic ratio in the uterine artery ranged from 40 to 75% (Fig. 2).

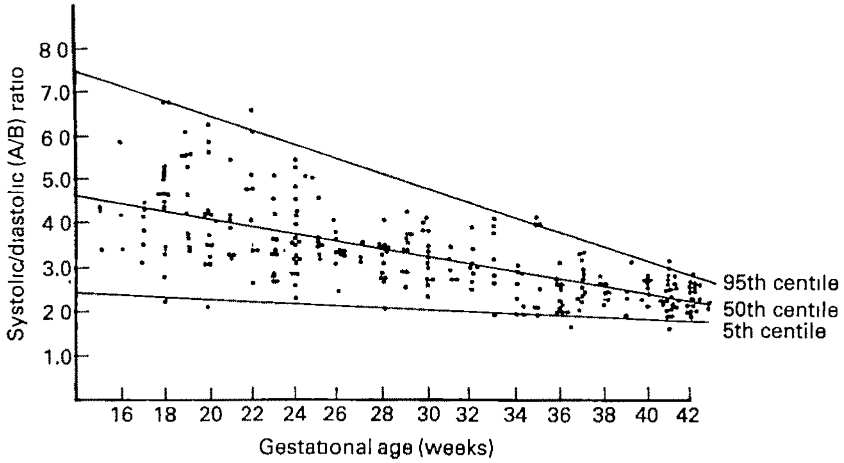

Fig. 1. Umbilical artery A/B ratios in 271 normal pregnancies between 16 and 42 weeks gestation The horizontal lines represent the 5th, 50th and 95th centile values.

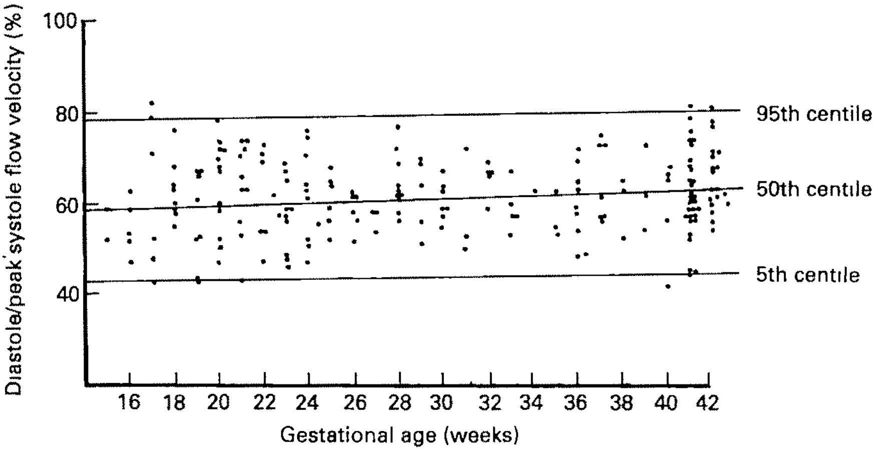

Fig. 2. Uterine artery diastolic/systolic velocity ratios estimated as a percentage in 271 normal pregnancies between 16 and 42 weeks gestation. The horizontal lines represent the 5th, 50th and 95th centile values.

Of the 71 complicated pregnancies, 38 had all three Doppler indices within the 5–95th centiles (the arterial flows were added to give one measurement for each fetus of combined cardiac output), five had abnormal recordings only from the uterine artery; 15 had abnormal recordings only from the umbilical artery; two had abnormal umbilical artery and combined cardiac output estimates; six had abnormal recordings from both umbilical artery and uterine artery; and five had all three indices abnormal. In no pregnancy was combined cardiac output alone abnormal. In nine pregnancies studied serially the A/B ratio of the umbilical artery trace became more abnormal as pregnancy advanced. The umbilical artery recordings in all the complicated pregnancies are shown in Fig. 3 in relation to the normal range.

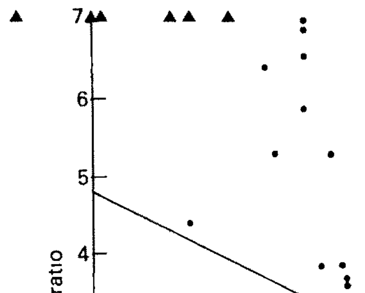

Fig. 3. Umbilical artery A/B ratios in 71 complicated pregnancies plotted against the normal range derived from the 271 normal pregnancies shown in Fig. 1. Fetal outcome is identified by the following symbols· ▲, Perinatal death; ●, other morbidity; ○, no morbidity.

The eventual outcome of the pregnancy was related to the antenatal Doppler findings. The obstetric staff in charge of management of these patients were not aware of the Doppler recordings, so the outcome was not influenced by the Doppler findings. Morbidity or an unfavourable outcome were defined as low birthweight (<10th centile according to Thomson *et al.* (1968)), cardiotocographic changes, signs of fetal distress during labour, a 5-min Apgar score of <7, a pH <7·23, elective delivery before 37 weeks gestation for other estimates of deteriorating fetal condition, or perinatal death. The results of the relation of the Doppler findings to morbidity are summarized in Table 1.

Of the 38 pregnancies with all Doppler indices normal, 29 ended in the birth of normal infants without any morbidity by our definition. Six others ended beyond 36 weeks gestation in the normal birth of infants that were small-for-gestation (<10th centile) but healthy The remaining three pregnancies had unfavourable outcomes In the first, fetal distress developed in early labour and the woman was delivered by emergency caesarean section. In the second, severe pregnancy-induced hypertension necessitated

Table 1. Relation between Doppler findings and fetal outcome in 71 complicated pregnancies

Doppler findings	*n*	Estimates of fetal morbidity: Total *n*	Perinatal death	Fetal distress: In pregnancy	Fetal distress: In labour	Low birthweight <10th centile	Elective birth <37 weeks	CS
Normal	38	9	0		2	9	3	2
Abnormal								
Umbilical artery only	15	13	0	1	4	10	8	8
Uterine artery only	5	3	0	1	1	0	3	1
Umbilical and uterine artery	6	6	0	1	1	6	4	4
Umbilical artery and CCO	2	2	2	1	0	2	1	0
Umbilical and uterine artery and CCO	5	5	4	2	0	5	3	2

CS, Caesarean section; CCO, combined cardiac output

elective caesarean section at 34 weeks; the third pregnancy was induced at 36 weeks gestation and fetal distress developed during labour. Thus, there were three pregnancies with false-negative predictions of associated fetal morbidity.

Of the 28 pregnancies with abnormal umbilical artery ratios, only two had a good outcome. These two pregnancies were complicated by mild pregnancy-induced hypertension superimposed on essential hypertension and the A/B ratios were only slightly abnormal. In the remaining 26 pregnancies there were six perinatal deaths; in all six, absent or reversed diastolic flow in the umbilical artery was detected before 30 weeks gestation; all these six pregnancies also had decreased combined cardiac output and four had abnormal uterine artery traces in addition. In 10 pregnancies the fetus developed either antenatal cardiotocographic changes or intrapartum fetal distress and five of these pregnancies required emergency surgical intervention. Of the 26 babies born in this group, two had low 5-min Apgar scores; 13 were electively born preterm, nine by caesarean section, 23 were small-for-gestation, 19 of them were below the 5th centile and 11 of these 19 had small calcified placentas that weighed less than normal for the gestational age (Thomson *et al.* 1969).

Of the five pregnancies where the uterine artery trace alone was abnormal three were induced before 37 weeks gestation but all five babies had birthweights appropriate for gestation.

Discussion

Our results for umbilical and uterine artery blood flow, both in the normal and abnormal pregnancies, are consistent with the results from other studies (Trudinger & Cook 1982; Trudinger *et al.* 1985*a*, *b*; Giles *et al* 1985; Campbell *et al.* 1983; Schulman *et al.* 1984).

Among the 32 complicated pregnancies that resulted in babies of low birthweight for gestational age, three groups can be identified. One group of six pregnancies had normal flow in both uterine and umbilical artery and a good outcome. The fetuses in this group are presumably healthy but have a low growth potential. The second group of 11 pregnancies had abnormal flow in both umbilical and uterine arteries and the outcomes in all of them were associated with morbidity by our definition. Six of the women in this group had severe proteinuric pregnancy-induced hypertension and the other five pregnancies were complicated by severe growth retardation. In these pregnancies, the primary disease is in the maternal uteroplacental bed and secondarily affects the fetus. The third group of 12 pregnancies had abnormal umbilical artery flow with normal uterine artery traces. Seven of these 12 pregnancies were complicated by severe growth retardation and five had proteinuric hypertension. That the seven growth-retarded pregnancies had normal readings from the uterine artery can be explained by the fact that the primary defect was on the fetal side of the placenta and was not maternal in origin. In the five women with pregnancy-induced hypertension the findings were contrary to expectation, since the primary disease is maternal. This may be explained by our failure in the early part of the study to sample multiple sites in the placenta. Differing flow velocity waveforms can be produced in different parts of the placental bed, therefore many sites should be sampled and the mean taken. This explanation may also account for the fact that two of the five pregnancies with abnormal uterine artery traces only had a good outcome.

The results suggest that serial Doppler assessment of high-risk pregnancies is of clinical value. Where all indices are normal, the outcome is likely to be good. Of 38 such pregnancies in our series, 35 had an uncomplicated outcome. The most reliable predictor of morbidity was the umbilical artery trace; only two of 28 pregnancies with abnormal traces had a normal outcome. An abnormal uterine artery tracing was of concern if found in combination with an abnormal umbilical artery A/B ratio. Thus, the uterine artery flow was less sensitive than the umbilical artery trace in predicting fetal morbidity. Although there are several sources of error in the calculation of cardiac output, reasonably reliable and reproducible results can be obtained (Allan *et al.* 1987). It appears from the results that the cardiac output is well maintained until late in the course of fetal compromise, as evidenced by the subsequent death of six of the seven fetuses in whom diminished combined cardiac output was found. A decreased cardiac output was never found without an abnormal umbilical artery trace. As the estimation of cardiac output is more difficult and time-consuming, it should be reserved for the further assessment of those pregnancies with an abnormal umbilical artery trace.

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References

Al-Ghazali, W., Chapman, M G., Chita, S K., Crawford, D. C. & Allan, L. D. (1987) Doppler assessment of umbilical artery blood flow for the prediction of outcome in fetal cardiac abnormality *Br J Obstet Gynaecol* **94**, 742-745

Allan, L. D. (1986) *Manual of Fetal Echocardiography,* MTP Press Ltd, Lancaster, pp. 56-59

Allan, L. D , Chita, S. K., Al-Ghazali, W., Crawford, D. & Tynan, M. (1987) Doppler echocardiographic evaluation of the normal human fetal heart *Br Heart J* **57**, 528-533

Campbell, S. (1976) Fetal growth. In *Fetal Physiology and Medicine* (Beard, R. W. & Nathanielsz, P. W., eds), W B. Saunders Co , Ltd, London, pp 271-301.

Campbell, S., Diaz-Racasens, J., Griffin, D. R., Cohen-Overbeek, T. E., Pearce, J. M., Wilson, K & Teague, M. J. (1983) New doppler technique for assessing uteroplacental blood flow *Lancet* **i**, 675-677.

Eik-Nes, S. H., Burbakk, A. O & Ulstein, M. (1980) Measurement of human fetal blood flow. *Br Med J* **280**, 283-284.

Eik-Nes, S. H , Marsal, K., Burbakk, A O , Kristoffersen, K. & Ulstein, M. (1982) Ultrasonic measurement of human fetal blood flow. *J Biomed Eng* **4**, 28-36.

Fitzgerald, D. E. & Drumm, J. E (1977) Non-invasive measurement of human fetal circulation using ultrasound, a new method *Br Med J* **ii**, 1450-1451

Fitzgerald, D. E , Stuart, B., Drumm, J E. & Duignan, N M. (1984) The assessment of the fetoplacental circulation with continuous wave Doppler ultrasound. *Ultrasound Med Biol* **10**, 371-376.

Giles, W B., Trudinger, B. J. & Baird, P. J. (1985) Fetal umbilical artery flow velocity waveforms and placental resistance· pathological correlation. *Br J Obstet Gynaecol* **92**, 31-38

Giles, W. B., Trudinger, B J & Cook, C. M. (1982) Fetal umbilical artery flow velocity time waveforms. *J Ultrasound Med* **1 (Suppl.)**, 98

Gill, R. W., Trudinger, B J , Garrett, W J , Kossoff, G. & Warren, P S (1981) Fetal umbilical venous flow measured in utero by pulsed Doppler and B-mode ultrasound. 1 Normal pregnancies *Am J Obstet Gynecol* **139**, 720-725.

Jouppila, P & Kirkinen, P. (1984) Umbilical vein blood flow as an indicator of fetal hypoxia. *Br J Obstet Gynaecol* **91**, 107-110.

Kirkinen, P., Jouppila, P & Eik-Nes, S. (1983) Umbilical vein blood flow in rhesus-isoimmunization. *Br J Obstet Gynaecol* **90**, 640-643.

McCallum, W. D., Williams, C S., Napel, S & Diagle, R B. (1978) Fetal blood velocity waveforms. *Am J Obstet Gynecol* **132**, 425-429.

Reed, K. L., Meijhoom, E. J , Sahn, D. J., Scagnelli, S A., Valdes-Cruz, L M. & Shenker, L. (1986)

Cardiac doppler flow velocities in human fetuses. *Circulation* **73**, 41-46.

Schulman, H., Fleischer, A., Stern, W., Farmakides, G., Jagani, N. & Blettner, P. (1984) Umbilical velocity wave ratios in human pregnancy. *Am J Obstet Gynecol* **148**, 985-990

Thomson, A. M., Billewicz, W. Z. & Hytten, F. E. (1968) The assessment of fetal growth. *J Obstet Gynaecol Br Commonw* **75**, 903-916.

Thomson, A. M , Billewicz, W. Z & Hytten, F E. (1969) The weight of the placenta in relation to birthweight. *J Obstet Gynaecol Br Commonw* **76**, 865-872.

Trudinger, B. J & Cook, C. M. (1982) Fetal umbilical artery velocity waveforms. *Ultrasound Med Biol* **8** **(Suppl. 1)**, 197.

Trudinger, B J., Giles, W. B., Cook, C. M., Bombardieri, J. & Collins, L (1985*a*) Fetal umbilical artery flow velocity waveforms and placental resistance: clinical significance. *Br J Obstet Gynaecol* **92**, 23-30

Trudinger, B. J , Giles, W B & Cook, C. M (1985*b*) Uteroplacental blood flow velocity-time waveforms in normal and complicated pregnancy. *Br J Obstet Gynaecol* **92**, 39-45

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Doppler ultrasound waveform indices: A/B ratio, pulsatility index and Pourcelot ratio

ROSEMARY S. THOMPSON, BRIAN J. TRUDINGER, COLLEEN M. COOK

Summary. Three different indices, the A/B ratio, the pulsatility index (PI) and the Pourcelot ratio (PR), are in common use for quantitative analysis of umbilical artery Doppler ultrasound waveforms. A detailed examination of the similarities and differences between these indices, together with the expected errors for each, was undertaken to enable informed comparisons and choices to be made. The indices were calculated from 133 last trimester recordings using an objective and very reliable computer analysis technique. The PI is more difficult to calculate than the other two quantities and the extra computation does not provide any extra information. The A/B ratio appears the simplest index to use but the values are not normally distributed. With the PR a normal distribution of values can be assumed. A theoretical consideration of errors showed that none of the indices is intrinsically less error prone for last trimester waveforms overall. The errors in the A/B ratio increase as the value of the index increase, whereas the converse holds for the PI and PR.

Doppler ultrasound velocity waveforms recorded from the umbilical artery can be used to assess fetal well-being. The earliest reports (McCallum *et al* 1978; Stuart *et al.* 1980; Giles *et al.* 1982) indicated that there were differences between waveforms recorded from normal and complicated pregnancies. Subsequent large studies by several independent investigators have confirmed this (Trudinger *et al.* 1985; Erskine & Ritchie 1985; Thompson *et al.* 1985; Schulman *et al.* 1984). Various different indices have been used for quantitative assessment of umbilical artery waveforms. The most commonly used indices are the A/B ratio (or systolic/diastolic ratio), the pulsatility index and the Pourcelot ratio (which is also referred to as the resistance index). A link between the waveform changes which occur in fetal compromise—as quantified by the A/B ratio—and raised placental resistance has been demonstrated (Giles *et al.* 1985; Trudinger *et al.* 1987).

The A/B ratio, pulsatility index (PI) and Pourcelot ratio (PR) all tend to decrease with advancing gestational age in normal pregnancy, but to increase in fetal growth retardation. Each index shows the same general behaviour and Thompson *et al.* (1986) showed a close correlation between all the indices for normal patients. However, some differences in the results for at-risk patients were noted. It was suggested that these could be due to differences between the indices in the underlying distribution of values for the normal population.

In this paper the relations between the three indices are examined in detail and the underlying distributions are investigated. The aim is to determine whether there are reasons to prefer the use of one particular index, or whether the

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Department of Obstetrics and Gynaecology, The University of Sydney at Westmead Hospital, Westmead, NSW 2145, Australia
ROSEMARY S. THOMPSON *Research Officer*
BRIAN J. TRUDINGER *Associate Professor*
COLLEEN M. COOK *Technical Officer*

Correspondence: Dr R S. Thompson

results are the same in practice whichever index is used. In this case there would no advantage in calculating all three indices, which has been the recent trend. The preferred index would be one which was easy to calculate, or less prone to error. Waveform indices do not measure a physical quantity and hence errors, in the sense of the difference between measured and true values, cannot be calculated. However, inaccuracies in estimating the true waveform dimensions will clearly lead to variations, or 'errors', in the values of the indices calculated from them. This intrinsic variability of an index, which should be distinguished from the many sources of variability encountered in practice, is examined in this paper. Simple geometrical shapes which resemble the umbilical artery waveform were used as a model and the errors in the indices calculated theoretically.

Patients and methods

Results from a total of 133 last trimester umbilical artery recordings are reported. Forty-eight normal pregnancies were examined at 36 weeks gestation and of these 12 were also studied serially at 2-week intervals from 30 through to 38 weeks gestation. In addition data from complicated pregnancies were obtained by examination of 17 patients (on 40 occasions) who were referred for study because of a suspected small-for-gestational-age infant. Other risk factors present in this group included maternal hypertension in five patients, poor obstetric history in one and abnormal renal function in another patient. The birthweight for each of these 17 patients was less than the 10th centile.

Doppler recordings and waveform analysis

The method for recording the Doppler signals and the computer analysis has been described (Trudinger *et al.* 1985; Thompson *et al.* 1985). Recordings were made using a directional continuous-wave Doppler with a 4 MHz transducer (Vasoflo, Sonicaid BV380 or Medasonics D10). The operator first located a loop of the umbilical cord with the assistance of a real-time scanner and then adjusted the Doppler transducer orientation to obtain maximum waveform amplitude and clarity. Real-time spectral analysis (Unigon Angioscan) was used. Good quality signals were stored on audio tape for off-line computer analysis. An acceptable signal should display the artefact free arterial waveform, together with the venous trace, for at least 5 s. It is essential that the signal be recorded during periods of fetal apnoea. Fetal breathing movements can be detected from modulations in the venous trace or during the averaging procedure of the computer analysis. This analysis used custom written software The maximum velocity waveform was extracted from the spectral data and an ensemble average of about eight waveforms was obtained. A smooth curve was then fitted to the averaged waveform and the required indices were calculated from this fitted curve (Thompson *et al.* 1985). This method is very reliable and is also resistant to the outlying data points which inevitably appear in clinical data. The set of indices obtained was transferred to a VAX 11/750 computer for statistical analysis (using Minitab Version 5.1).

Errors

Small measurement errors in the waveform dimensions can result in errors in the indices. These errors were investigated theoretically using three geometrical shapes which resemble the umbilical artery waveform—an offset triangle and two sine curves (full wave and half wave), also with positive offsets. The actual values of the A/B ratio, PI and PR were calculated together with the percentage errors expected for small errors in the two critical measurements—the peak systolic velocity level (A) and the least diastolic velocity level (B).

Results

The A/B ratio, PI and PR were calculated according to the definitions shown in Fig. 1, and the correlation coefficients for the three possible pairs of indices were obtained. The results are summarized in Table 1. All the r values are greater for the normal patients ($n = 93$) than for the whole group ($n = 133$). There are two sets of figures given for the whole group because of the problems presented by those A/B values which approach infinity. (This occurs for abnormal waveforms if the diastolic flow level approaches zero.) For the first set the A/B ratio scale was truncated at 10, and those studies with higher values omitted from the calculation of all three correlation coefficients. For the second set the A/B values returned by the computer programs were used, with only ∞ coded as a missing value.

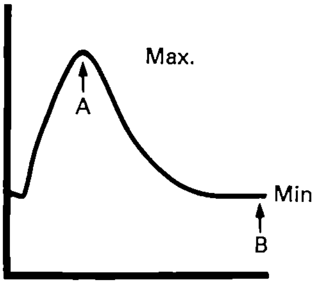

Fig. 1. Definition of three waveform indices.

Pulsatility index (PI) $= \frac{A - B}{\text{Mean}}$

Pourcelot ratio (PR) $= \frac{A - B}{A}$

A/B ratio = systolic/diastolic ratio.

The computer method used derives the indices from a curve fitted to the data by a least squares algorithm (Thompson *et al.* 1985). This method can generate A/B values in a range where less detailed forms of analysis would be unable to assign a value other than infinity. There are only four such very high A/B values in this study, but they have an enormous effect on the A/B ratio correlation coefficients. These very high A/B values will also be subject to large percentage errors (see below). For these reasons, the *r* values calculated with the A/B ratio scale truncated at 10 were included for comparison.

A/B ratio and Pourcelot ratio

From the definitions of these two quantities it can be seen that they are related by the equation

$$PR = 1 - \frac{1}{A/B}$$

where $1 < A/B < \infty$ and $0 < PR < 1$ (see Fig. 2). This is an exact relation, but it is non-linear. The correlation coefficients given in Table 1 are <1 because of this non-linearity. The *r* value was largest for the normal group because the graph of PR versus A/B more closely approximate a straight line if only a small range of low values is considered. The *r* value shown for all patients in part (b) in Table 1 is substantially less than the value in part (a) because the four values in the extremely non-linear upper tail ($AB \rightarrow \infty$, $PR \rightarrow 1$) are included. Thompson *et al.* (1986) reported that the PR tended to classify as normal a small number of waveforms from at-risk patients (about 10%) which were classified as abnormal by the A/B ratio. (The normal range was taken as the mean ± 2SD values.) The normal ranges for both indices were calculated under the assumption that the data represented random samples from normally distributed underlying populations. However, the non-linear relation between the A/B ratio and PR indices means that if this is true for one index, it cannot also be true for the other.

A/B ratio and pulsatility index

The correlation coefficients for the A/B ratio and the PI were equal to or greater than those found for the A/B and PR values. There was no exact relation between the A/B ratio and the PI. The scatter of points introduced by this factor would tend to decrease the *r* value, but this was offset by the increase resulting from the more nearly linear relation between them. This can be seen in Fig. 3, where the PI is plotted against the A/B ratio for the normal patients (Fig. 3a) and for all patients (Fig. 3b). (The A/B ratio scale has been truncated at 10 in Fig. 3b, and those points with A/B values >10 are shown at A/B = 10. Note that the PI values do have an absolute upper limit, but it is not approached in practice.)

Table 1. Correlation coefficients for the A/B ratio, pulsatility index (PI) and Pourcelot ratio (PR)

Patient group		Correlation coefficient (*r*) A/B	 PI
Normal (*n* = 93)	PI	0·958	
	PR	0·958	0·977
All patients (*n* = 133)			
(a) Excluding 13 results where A/B ratio >10	PI	0·909	
	PR	0·892	0·979
(b) Excluding 9 results where A/B ratio = ∞	PI	0·625	
	PR	0·510	0·937

The large differences in the correlation coefficients between (a) and (b) are due to four extremely high values (see text)

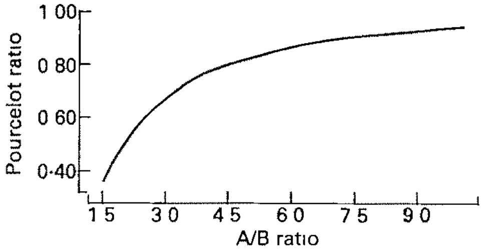

Fig. 2. Relation between the Pourcelot ratio (PR) and the A/B ratio

Although the PI versus the A/B ratio curve deviates from a straight line, especially at the upper end of the scale, the relation between them is closer to linear over more of the range of values than for the A/B ratio and PR. This suggests that the underlying distributions for the A/B ratio and the PI are more similar in shape, and Thompson *et al.* (1986) found that waveforms obtained from at-risk patients were almost always classified the same by the A/B ratio and the PI.

The A/B ratio and the PI are not related by an exact equation because the PI involves calculation of the mean value of the waveform envelope (see Fig. 1). If widely different PI values could be obtained from waveforms with the same A and B values, a wide scatter of points about the general trend line would be evident in Fig. 3. This was not the case. There was very little scatter and the correlation coefficient for the A/B ratio and the PI was as high or higher than that for the A/B ratio and PR. The tendency for slightly increased scatter towards the upper end of the A/B ratio versus the PI graph is probably due to the large errors expected for high values of the A/B ratio (see below).

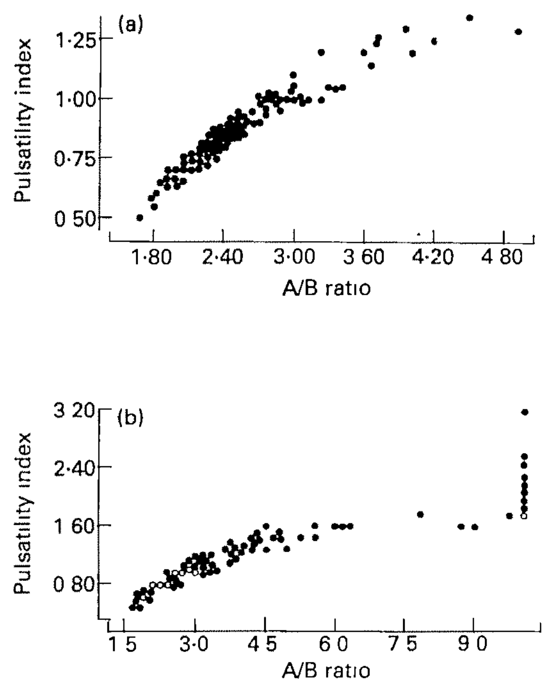

Fig. 3. (a) Pulsatility index plotted against the A/B ratio for normal patients ($n = 93$). (b) Pulsatility index plotted against the A/B ratio for all patients ($n = 133$). An open circle (○) has been used to indicate five or more coincident points, and points with off-scale A/B values (>10) have been drawn at 10

Pulsatility index and Pourcelot ratio

There is no exact relation between the PI and the PR but these were the most highly correlated pair of indices (see Table 1). Plotting one against the other showed a small scatter of points and an underlying relation which was very close to linear except when PR → 1 (Thompson *et al.* 1986).

Underlying distributions

The underlying distributions for each index were investigated using the 48 normal studies recorded at one gestational age (36 weeks). Figure 4a shows the histogram of the A/B values together with the normal probability density function having the appropriate mean and standard deviation. Figures 4b and 4c show the same information for the PI and PR respectively.

The normality assumption was tested using the Shapiro–Wilk test (as implemented by Minitab version 5.1). For this test the correlation coefficient for the normal probability plot is calculated. The value for the A/B ratio was low enough for it to be concluded that this population is not normally distributed ($P<0{\cdot}01$). The result for the PR was consistent with normality whereas a borderline result was obtained for the PI. The correlation coefficient ($r = 0{\cdot}983$) was almost small enough for rejection of the normality hypothesis at $P = 0{\cdot}10$. The normality assumption was also tested using the less satisfactory χ^2 test. The expected frequencies were calculated from the appropriate normal cumulative distribution functions, with cell sizes chosen to ensure the expected frequencies were greater than 5. (There was one exception.) This test did not give conclusive results. The normality assumption could be rejected for the A/B values only at $P<0{\cdot}10$. For both the PI and PR the χ^2 values were not large enough to reject

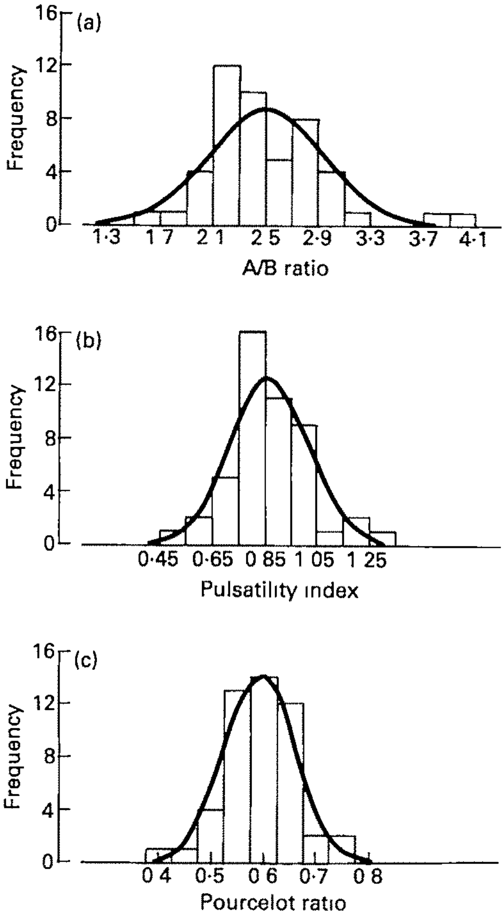

Fig. 4. Histogram of values at 36 weeks gestation compared to the normal probability density function with appropriate mean and standard deviation. (a) A/B ratio; (b) pulsatility index; (c) Pourcelot ratio

normality, nor were they small enough to provide strong evidence of normality

Errors

The three theoretical waveform shapes considered are shown in Fig. 5. Exact formulas for the PI in terms of A (the maximum systolic value of the waveform) and B (the least diastolic value) can be derived for each. For waveform types (a) and (b)

$$\mathrm{PI} = 2\,(\mathrm{A}-\mathrm{B})/(\mathrm{A}+\mathrm{B})$$

and for (c)

$$\mathrm{PI} = \pi\,(\mathrm{A}-\mathrm{B})/(2\mathrm{A}+[\pi-2]\mathrm{B}).$$

Four sets of A and B values, corresponding to waveforms ranging from normal through to abnormal, were chosen. The values of the A/B ratio, PI and PR indices were calculated. Small measurement errors of ±1 unit in A and ±1 unit in B were assumed and the resulting percentage errors in each of the three indices were calculated. The units for A and B were chosen for consistency with the frequency resolution of the spectrum analyser (see Appendix). The calculated percentage errors in the indices are given in Table 2. The results for the A/B ratio and the PR were the same for all three waveform shapes, since these indices depend only on A and B. For the PI the results for the half sine wave (Fig. 5c) were different from the other two. The results in Table 2 show that errors of 10% or more in all the indices can result from small measurement errors in A and B. Overall, none of the three indices is intrinsically less prone to error than the others for last trimester waveforms.

The percentage errors in A/B increase as the waveform becomes abnormal, i.e. as the actual A/B value increases. The converse is true for both the PI and the PR and so the largest errors for these indices are expected with normal waveforms. The results in Table 2 show that the error associated with the A/B ratio at a value of 6 is very large (17·5%). This A/B value is abnormally high for a third trimester waveform, but during the second trimester such values can occur in normal pregnancy (Erskine & Ritchie 1985).

Discussion

Pairwise comparisons of the A/B ratio, PI, and PR were made. The correlation coefficients were high for all possible pairs, especially if only normal patients were considered. The values reported in Table 1 are very close to those given previously (Thompson *et al.* 1986) for a smaller number of studies. The correlation coefficient is a measure of the linear relation between two variables. The relation between the A/B ratio and the PR is exact but it is not linear (Fig. 2) and the correlation coefficient is therefore less than unity. There is no exact relation between the A/B ratio and the PI, or between the PR and the PI, but the correlation coefficients for both these pairs of indices are higher than the corresponding value for the A/B ratio and the PR. The correlation coefficient reflects both the scatter of points about the 'best fit' line and the curvature of this line. The scatter of points is so small for these indices that the correlation coefficients

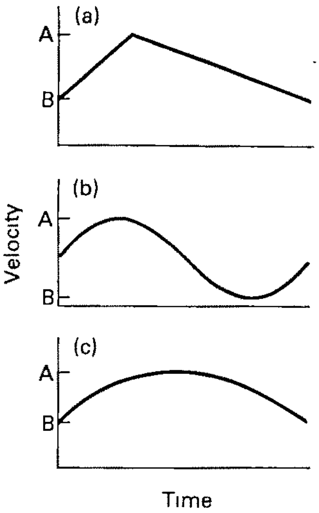

Fig. 5. Theoretical waveform shapes for examination of the effects of measurement errors in A and B on the calculated indices. (a) Triangle with offset A; (b) full sine wave with offset (A + B)/2; (c) half sine wave with offset A. In each case A is the maximum height of the waveform above the zero level and B is the minimum height above the zero level.

reflect mainly the departure from linearity of the underlying relation.

The PI requires calculation of the mean value of the waveform envelope over the cardiac cycle and it has been asserted that it should therefore give more information than indices obtained using only the maximum (A) and minimum (B) points of the envelope. If this were so there would be a wide range of PI values for any given A/B ratio. The very small scatter of points in the PI versus A/B graph (Fig. 3) shows that this is not the case. These results show that the extra computation involved in obtaining the PI does not give any extra information about the umbilical artery waveform. This conclusion may not hold for waveforms recorded from other vascular sites (e.g. fetal aorta) which are more variable in shape than the umbilical artery waveforms. However, it cannot automatically be assumed that the PI is then the preferred index. This is because the increased variability in waveform shape, and consequently in PI values, may not be due to the physiological factor(s) of interest.

The non-linearity (curvature) evident when any of the indices is plotted against another means that they cannot all be normally distributed. Sufficient data to test for normality of the underlying distributions were obtained at one gestational age (36 weeks). It was found that the distribution of A/B values was skewed to the right and cannot be assumed normal in shape. The results for the PR were consistent with normality, while intermediate and inconclusive results were obtained for the PI. The true 95th

Table 2. Values and percentage errors for the A/B ratio, pulsatility index (PI) and Pourcelot ratio (PR) for four typical A and B values with measurement errors of ± 1 unit in both A and B

	Value of index	Percentage error in index with Δ A = ± 1 and Δ B = ± 1
A = 40	A/B = 2	7·5%
B = 20	PI = 0·67 (a) and (b)	13·3%
	= 0·61 (c)	13·1%
	PR = 0·5	12·5%
A = 40	A/B = 3	10·0%
B = 40/3	PI = 1·0 (a) and (b)	11·25%
	= 0·88 (c)	10·8%
	PR = 0·67	10·0%
A = 40	A/B = 4	12·5%
B = 10	PI = 1·2 (a) and (b)	10·7%
	= 1·03 (c)	10·1%
	PR = 0·75	9·2%
A = 40	A/B = 6	17·5%
B = 40/6	PI = 1·43 (a) and (b)	10·3%
	= 1·2 (c)	9·6%
	PR = 0·83	8·5%

These are theoretical results for the waveform shapes shown in Fig 5. The A and B values are appropriate to umbilical artery waveforms (see Appendix). The first PI result is for waveform shapes (a) and (b), the second for (c).

centile lines for the A/B ratio, and probably also the PI, are higher than those calculated using the mean and standard deviation under the assumption of normality. The data so far suggest that for the A/B ratio the magnitude of the error at 36 weeks is less than 10%. (This can be estimated from the cumulative frequency plot more readily than from the histogram shown in Fig. 4.) The correction required is not large, especially considering the magnitude of the expected errors, but it should be taken into account to avoid discrepancies between the indices.

It is also possible to estimate the true 95th centile for the A/B ratio by first analysing the PR values and then transforming using the equation A/B = 1/(1−PR). This method also indicates that the increase in the 95th centile value is less than 10% for last trimester waveforms. Larger increases can be expected for earlier second trimester results, where the departure from normality of the A/B values becomes more marked (Thompson *et al.* 1988).

Variations in the values calculated for any waveform index can be expected for several reasons. There may be true moment-to-moment variation in the recorded waveform for physiological reasons. Apart from this, any non-objective technique for calculating indices will result in inter- and intra-observer variations for repeated measurements on the same data. The indices in this paper were all calculated by an objective computer method which always returns the same values for the same input data. Even so, this does not guarantee error-free indices as the programs may consistently over- or underestimate some waveform dimensions. The effect of measurement errors of this sort on the calculated waveform indices was considered theoretically. These errors are the minimum expected from any form of waveform analysis. It was shown that small and quite realistic errors in the waveform dimensions consistently lead to errors of 10% or more in the indices. None of the indices is intrinsically less error prone if normal or near normal third trimester waveforms are considered. The A/B ratio suffers from larger percentage errors than do the other two indices at the higher values typical of abnormal third trimester or normal second trimester waveforms. This could contribute to the extremely large variance reported for normal second trimester A/B ratio values (Erskine & Ritchie 1985).

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References

Erskine, R. L. A & Ritchie, J. W. K (1985) Umbilical artery blood flow characteristics in normal and growth retarded fetuses. *Br J Obstet Gynaecol* **92,** 605-610.

Giles, W. B., Trudinger, B J. & Cook, C. M (1982) Fetal umbilical artery velocity waveforms *J Ultrasound Med* **1 (Suppl.),** 98

Giles, W. B., Trudinger, B. J. & Baird, P. J. (1985) Fetal umbilical artery flow velocity waveforms and placental resistance. Pathological correlation *Br J Obstet Gynaecol* **92,** 31-38

Gill, R. W , Trudinger, B. J , Garrett, W. J., Kossoff, G. & Warren, P. S. (1981) Fetal umbilical venous flow measured *in utero* by pulsed Doppler and B-mode ultrasound. 1. Normal pregnancies *Am J Obstet Gynecol* **139,** 720-725.

McCallum, W. D., Williams, C. S., Napel, S. & Daigle, R. E. (1978) Fetal blood velocity waveforms *Am J Obstet Gynecol* **132,** 425-429

Schulman, H., Fleischer, A., Stern, W., Farmakides, G., Jagani, N. & Blattner, P. (1984) Umbilical velocity wave ratios in human pregnancy *Am J Obstet Gynecol* **148,** 986-990

Stuart, B., Drumm, J., FitzGerald, D. E. & Duignan, N. M. (1980) Fetal blood velocity waveforms in normal pregnancy *Br J Obstet Gynaecol* **87,** 780-785.

Thompson, R. S , Trudinger, B. J. & Cook, C M. (1985) Doppler ultrasound waveforms in the fetal umbilical artery: Quantitative analysis technique. *Ultrasound Med Biol* **11,** 707-718

Thompson, R S , Trudinger, B. J & Cook, C. M. (1986) A comparison of Doppler ultrasound waveform indices in the umbilical artery I Indices derived from the maximum velocity waveform *Ultrasound Med Biol* **12,** 835-844

Thompson, R. S , Trudinger, B. J., Cook, C M & Giles, W. B. (1988) Umbilical artery velocity waveforms: Normal reference values for the A/B ratio and Pourcelot ratio. *Br J Obstet Gynaecol* **95,** 589-591.

Trudinger, B. J., Giles, W. B., Cook, C M., Bombardieri, J. & Collins, L (1985) Fetal umbilical artery flow velocity waveforms and placental resistance: clinical significance. *Br J Obstet Gynaecol* **92,** 23-30.

Trudinger, B. J., Stevens, D., Connelly, A., Hales, J. R., Alexander, G., Bradley, L., Fawcett, A. & Thompson, R. S. (1987) Umbilical artery flow velocity waveforms and placental resistance· the effects of embolization of the umbilical circulation. *Am J Obstet Gynecol* **157**, 1443-1448.

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Appendix

Choice of units for error calculations

Most umbilical artery waveforms have A/B values in the range from 2 (normal, late third trimester) to about 6 (abnormal third trimester, normal early second trimester). This is the range of A/B values covered by the data in Table 2. The actual A and B values were chosen so that one unit of A (or B) would correspond to one step in the discrete frequency scale of the spectrum analyser when operated in the frequency range appropriate for umbilical artery waveforms. The values used in the following calculation were chosen to represent the worst case for errors, i.e. the waveform with the lowest Doppler frequency shift. The Doppler frequency shift is given by

$$f_D = \frac{2fv\cos\theta}{c}$$

where f is the frequency of the transmitted ultrasound,

v is the velocity of the scatterer,

θ is the angle between the ultrasound beam and the vessel axis, and

c is the speed of sound in tissue.

The transducer frequency was $f = 4$ MHz and the value $c = 1540$ m/s was assumed. The Doppler angle was taken to be $\theta = 60°$, since good Doppler signals cannot be obtained for higher angles. The time averaged volume flow rate in the umbilical vein is approximately 120 ml/min in the early third trimester (Gill *et al.* 1981). The corresponding (time averaged) mean velocity in each umbilical artery would be 32 cm/s for an arterial diameter $d = 0{\cdot}2$ cm, or 127 cm/s for $d = 0{\cdot}1$ cm. Further assuming that the instantaneous maximum velocity at peak systole V is roughly twice this mean value gives

$$(f_D)_{\max} = 6{\cdot}5 \text{ kHz for } V = 250 \text{ cm/s, and}$$
$$(f_D)_{\max} = 1{\cdot}6 \text{ kHz for } V = 60 \text{ cm/s.}$$

The frequency resolution of the spectrum analyser (Unigon Angioscan) is 40 Hz on the 5 kHz range setting (the lowest). Thus A = 40 corresponds to a waveform of maximum frequency shift 1·6 kHz. Errors of ±1 unit in A or B therefore represent true minimum measurement errors for the discrete frequency scale. Taking the values A = 40 and B = 20 (for A/B = 2) gives the worst possible case consistent with the above f_D calculations, since the percentage errors are smaller (for the same A/B value) if the actual A or B values are larger.

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Umbilical artery velocity waveforms: normal reference values for A/B ratio and Pourcelot ratio

ROSEMARY S. THOMPSON, BRIAN J. TRUDINGER,
COLLEEN M. COOK, WARWICK B. GILES

Summary. Normal reference values for the umbilical artery Pourcelot ratio and A/B ratio are reported. Thirty-five normal patients were studied serially from 20 weeks to term. The A/B ratio centiles were corrected for non-normality of the underlying distribution by transforming from the Pourcelot ratio values. The correction needed was small during the last trimester, but larger for second trimester data. Of the 35 patients 24 were nulliparous and there was a slight tendency for the waveform indices to be higher in the nulliparae, but the numbers in this study were too small to be conclusive about the effect of parity.

There are three main indices in use for assessment of Doppler ultrasound umbilical artery waveforms. These are the A/B (or systolic/diastolic) ratio, the pulsatility index (PI) and the Pourcelot ratio (PR). Indices are generally derived from the maximum velocity waveform, i.e. the envelope of the sonogram. A recent comparative study showed that these three indices are highly correlated (Thompson *et al.* 1988). The A/B ratio and the PR depend only on A (the maximum systolic velocity level) and B (the least diastolic velocity level) and are related by the equation $A/B = 1/(1-PR)$. The correlation coefficient for these two indices is less than 1 because the relation between them, although exact, is not linear.

Normal reference values for the A/B ratio have been published by several groups (Stuart *et al.* 1980; Schulman *et al.* 1984; Trudinger *et al.* 1985; Erskine & Ritchie 1985) and normal PR values have been given by Thompson *et al.* (1986) and Erskine & Ritchie (1985). For each of these reports the normal range for the index, expressed using either ± 2 SD or 95th and 5th centiles, was calculated from the mean and standard deviation of the data under the assumption that they represented a random sample from a normally distributed population. Thompson *et al.* (1988) have shown that this can be invalid for the A/B ratio, and probably also the PI. The purpose of this paper is to report normal A/B and PR reference values for a larger group of patients studied serially from 20 weeks. The A/B range was corrected for the non-normality of the underlying distribution.

Patients and methods

The results reported were obtained from 35 normal patients who were studied from 20 weeks. Most of them were studied at 2-week intervals from 28 weeks to term, and a smaller number were also studied at 20 and 24 weeks gestation (Table 1). There were no maternal or fetal risk factors present for any patient in the group. Of the 35 patients 24 were nulliparous and 11 were parous (four para 1, six para 2 and one para 3). Gestational ages were known from certain dates and there was ultrasound con-

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Department of Obstetrics and Gynaecology, The University of Sydney at Westmead Hospital, Westmead, NSW 2145, Australia
ROSEMARY S. THOMPSON *Research Officer*
BRIAN J. TRUDINGER *Associate Professor*
COLLEEN M COOK *Technical Officer*
WARWICK B GILES *Staff Specialist*

Correspondence· Dr R S Thompson

Table 1. The Pourcelot ratio from 20 to 40 weeks gestation

Gestational age (weeks)	*n*	Pourcelot ratio	
		Mean	(SD)
20	15	0·746	(0·056)
24	18	0·711	(0·051)
28	26	0·683	(0·044)
30	32	0·641	(0·057)
32	32	0·630	(0·055)
34	34	0·611	(0·068)
36	34	0·556	(0·060)
38	32	0·537	(0·056)
40	18	0·518	(0·049)

firmation in many patients. All patients were delivered spontaneously after 37 weeks gestation and the birthweights were all greater than the 10th centile. Any patient studied who subsequently failed to meet all these requirements was excluded from the group reported here. (Exclusions due to hypertension and premature labour occurred in practice.)

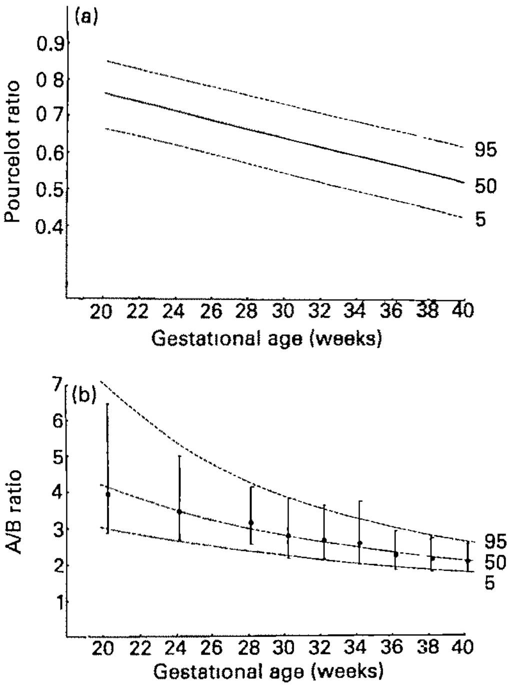

Fig. 1. (a) Pourcelot ratio normal reference values The 95th, 50th and 5th centiles were calculated from the data in Table 1 and regression lines fitted to each. (b) A/B ratio normal reference values The 95th, 50th and 5th centiles shown at each gestational age were calculated from the corresponding PR values using A/B = 1/(1−PR). The broken lines are the PR regression lines shown in (a) similarly transformed.

The study technique used was the same as described previously by Trudinger *et al.* (1985). A 4 MHz continuous-wave Doppler transducer was used and recordings were made only during periods of fetal apnoea The waveform was displayed after real-time spectral analysis and a hard copy of at least 5 s duration was obtained using an oscilloscope recorder. The A/B ratio was measured by hand and an average value, incorporating at least five consecutive cardiac cycles, was calculated.

Results

The PR results for all patients are summarized in Table 1. At each gestational age both the A/B and PR values were checked for normality using a test based on the correlation coefficient of the normal probability plot (Minitab's implementation of the Shapiro–Wilk test). There was no gestational age for which the PR values were not normally distributed. The correlation coefficients for the PR were always greater than for the corresponding A/B values, and it has been shown previously that third trimester A/B values are not normally distributed (Thompson *et al.* 1988). However, the number of patients in this study was small and the A/B ratio normality tests were significant only at $P<0{\cdot}10$ for 20, 24, 30 and 32 weeks gestation.

The 50th, 95th and 5th centiles for the PR at each gestational age were calculated from the data in Table 1. Regression lines were then fitted to each set of centile values and the results are shown in Fig. 1a. The lines in Fig. 1b for the A/B centiles (95th, 50th and 5th) were obtained directly from the corresponding PR regression lines by using the equation A/B = 1/(1−PR). The actual A/B centile values at each gestational age are also shown in Fig. 1b. The decrease of the A/B ratio with gestational age is better fitted by this curve than by a straight line. (The curves are hyperbolic functions of gestational age since they are PR regression lines.)

The A/B centile values at each gestational age shown in Fig. 1b are also shown in Fig. 2 (unbroken lines). These are the values obtained by transforming the mean ± 1·645 SD PR values according to the equation A/B = 1/(1−PR). The broken lines in Fig. 2 show the results which are obtained using raw A/B values and assuming a

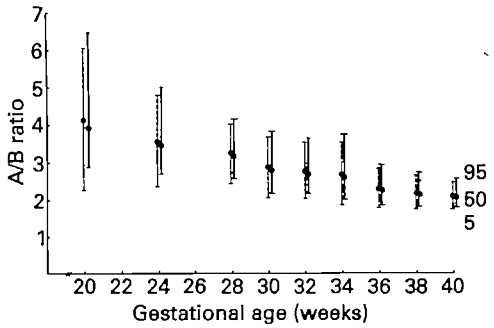

Fig. 2. A/B ratio normal reference values. The centiles calculated by transforming from the PR values are shown by the unbroken lines (as in Fig 1b) The results obtained directly from the A/B values (broken lines) underestimate both the 95th and 5th centiles.

normal distribution. This leads to underestimation of both the 95th and 5th centiles, and the error increases at earlier gestational ages.

The effect of parity on the PR values was considered using the two-sample *t*-test. The mean PR values for the nulliparous group were observed to be higher than the mean for the parous group at each gestational age except one (24 weeks), but the difference was not statistically significant except at 30 weeks, where $P<0.01$. The power of this test for the effect of parity was very low because of the small numbers in this study. The power, estimated according to the method described in Zar (1984), was found to be less than 30% (at $P = 0.05$) in all cases.

Discussion

Measurement of A and B permits calculation of both the A/B ratio and the PR, and these indices are related by the equation $A/B = 1/(1-PR)$. The A/B ratio values are not always found to be normally distributed, whereas the PR values are. In this case the true centiles (e.g. 95th) for the A/B values can be obtained by first working out the PR results and then transforming back to the A/B values using the above equation.

The results in Fig. 2 show the error in the A/B 95th and 5th centile lines introduced by assuming a normal distribution. Throughout the third trimester the error is slight—less than 10% in all cases. With second trimester data the departure of the A/B values from normality becomes more marked and the error increases. In this study the normality assumption for the A/B ratio could not be rejected for gestational ages 34 weeks and greater, but it has been demonstrated with a larger number of patients (studied at 36 weeks) that last trimester A/B values are not necessarily normally distributed (Thompson *et al.* 1988).

The number of parous patients in this study was small (less than one third of the total), and the effect of parity could not be conclusively assessed. Overall, there was no significant difference between the parous and nulliparous patients, but a tendency towards lower PR (and A/B) values in parous patients was noted.

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References

Erskine, R. L. A. & Ritchie, J. W K. (1985) Umbilical artery blood flow characteristics in normal and growth retarded fetuses *Br J Obstet Gynaecol* **92**, 605-610.

Schulman, H., Fleisher, A , Stern, W , Farmakides, G., Jagani, N & Blattner, P. (1984) Umbilical velocity wave ratios in human pregnancy. *Am J Obstet Gynecol* **148**, 985-990.

Stuart, B., Drumm, J., FitzGerald, D. E & Duignan, N M (1980) Fetal blood velocity waveforms in normal pregnancy. *Br J Obstet Gynaecol* **87**, 780-785

Thompson, R. S., Trudinger, B J & Cook, C M. (1986) A comparison of Doppler ultrasound waveform indices in the umbilical artery. I. Indices derived from the maximum velocity waveform. *Ultrasound Med Biol* **12**, 835-844

Thompson, R. S., Trudinger, B. J. & Cook, C. M. (1988) Doppler ultrasound waveform indices A/B ratio, pulsatility index and Pourcelot ratio. *Br J Obstet Gynaecol* **95**, 581-588

Trudinger, B J , Giles, W. B., Cook, C. M , Bombardieri, J. & Collins, L (1985) Fetal umbilical artery flow velocity waveforms and placental resistence: clinical significance *Br J Obstet Gynaecol* **92**, 23-30

Zar, J. H. (1984) *Biostatistical Analysis*. Prentice-Hall, Englewood Cliffs, NJ. p 137

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The effect of the antiprogestin mifepristone (RU 486) on maturation and in-vitro fertilization of human oocytes

IOANNIS E. MESSINIS, ALLAN TEMPLETON

Summary. The effect of RU 486 (mifepristone), a potent antiprogestin, on the in-vitro fertilization of human oocytes was investigated. In 40 normal volunteer women requesting laparoscopic sterilization, follicle aspiration for oocyte recovery was attempted 34 h after the injection of 5000 i.u. human chorionic gonadotrophin (hCG). Twenty women were allocated to receive 100 mg RU 486 orally 1 h before the hCG injection, the remaining 20 women acted as controls. There was no significant difference in the cleavage rate of the ooctyes after fertilization *in vitro* between the two groups (56% and 66% respectively). Also, the morphological characteristics of the cleaving oocytes and the concentrations of oestradiol, progesterone and androstenedione in the follicular fluid of the leading follicle did not differ significantly between the two groups. Since RU 486 was detected in substantial amounts in the follicular fluid specimens, these results suggest that progesterone is not critical for the final stages of human oocyte maturation.

The role of intrafollicular sex steroids in the maturation of human oocytes is not clear. Carson *et al.* (1982) have reported that oestrogenic follicles contain eggs with the potential for fertilization *in vitro* and give rise to pregnancy after embryo transfer (ET). Also, an association between high levels of oestradiol (E2) and progesterone in the follicular fluid and the ability of the oocyte to undergo fertilization *in vitro* has been reported (Wramsby *et al.* 1981). Although these results were confirmed later by other studies (Fishel *et al.* 1983; Botero-Ruitz *et al.* 1984), more recent data have failed to show any significant difference in the levels of E2 and progesterone between follicles yielding fertilizable and non-fertilizable oocytes *in vitro* (Hillier *et al* 1985; Uehara *et al.* 1985). It is obvious that these studies deal mainly with the assessment of intrafollicular sex steroids as indices of the fertilizability and developmental potential of the oocytes *in vitro*, while the possibility that these steroids are involved in the process of in-vitro maturation of human oocytes is neither confirmed nor excluded.

Recently, a new synthetic steroid, RU 486 (17β-hydroxy-11β-(4-dimethylamino-phenyl)-17α-(1-propynyl)-estra-4,9-diene-3-one; mifepristone, Roussel-Uclaf, France), has become available, which acts as a progesterone and glucocorticoid antagonist at the receptor level. This compound induces menses or abortion in women treated during the luteal phase or in early pregnancy (Herrmann *et al.* 1982; Kovacs *et al.* 1984) and in castrated monkeys during treatment with E2 and progesterone (Healy *et al.* 1983).

The present study was undertaken to investigate the role of progesterone in the maturation of human oocytes by examining the effect of the

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Department of Obstetrics and Gynaecology, University of Aberdeen, Foresterhill, Aberdeen AB9 2ZD, Scotland
IOANNIS E. MESSINIS *Senior Lecturer*
ALLAN TEMPLETON *Professor*

Correspondence. I. E. Messinis

RU 486 on the ability of the oocytes to fertilize and develop *in vitro*.

Patients and methods

The study included 48 healthy, parous women requesting laparoscopic sterilization who volunteered to participate. All had normal menstrual and medical past history and gave written informed consent. A fixed treatment regimen, described previously (Messinis *et al.* 1986), was used to stimulate follicular growth. Starting on day 21 of a spontaneous cycle, norethisterone was given to each woman for 7 to 14 days (10 mg/day) in order to adjust the time of onset of menses. A 5-day course of treatment with clomiphene (Serophene, Serono Labs Ltd) was then given to the women (150 mg/day) starting 7 days after the end of norethisterone administration. All women were admitted on day 16 and human chorionic gonadotrophin (hCG, 5000 i.u., Profasi, Serono Labs Ltd) was injected intramuscularly at 22.30 hours on the same day.

The 48 women were alternately allocated to receive treatment with RU 486 (24 women) or not to receive treatment (24 women). RU 486 was given as a single oral dose of 100 mg 1 h before the hCG injection. Laparoscopy for tubal sterilization and oocyte recovery was performed 34 h after the hCG injection, i.e. at 8.30 hours on day 18. At laparoscopy all follicles >15 mm in diameter were aspirated.

An aliquot of each follicle aspirate was stored at −20°C for subsequent measurement of E2, progesterone and androstenedione. The recovered eggs were inseminated using donor semen as described by Templeton *et al.* (1984).

Table 1. Comparison of recovery and cleavage rates of oocytes between women treated with RU 486 and controls

	Control	RU 486
Number of women		
Who had a laparoscopy	24	24
Ovulated before laparoscopy or did not respond to treatment	4	4
In whom follicle aspiration was attempted	20	20
Number of follicles aspirated (>15 mm)	46	39
Number of eggs		
Recovered (per cent of follicles aspirated)	36 (78)	32 (82)
Fertilized/cleaved (per cent of recovered eggs)	24 (66)	18 (56)

Hormone assays

E2 was measured in follicular fluid samples using a radioimmunoassay kit (SB-ESTR) purchased from CIS (Italy). Progesterone was measured with the Amerlex-M progesterone RIA kit (Amersham, UK) and androstenedione was measured with a radioimmunoassay kit purchased from Steranti Research Ltd (Switzerland). Serum cortisol was measured using the Corti-cote kit manufactured by Becton Dickinson. Values for E2, progesterone and androstenedione are expressed as ng/ml and for cortisol as nmol/l. Inter-assay and intra-assay coefficients of variation for E2, progesterone, androstenedione and cortisol were 8·6% and 5·4%, 9·8% and 7·6%, 7·0% and 7·0% and 4·0% and 5·0% respectively.

Statistical analysis

For statistical assessment the unpaired Student's *t*-test and the χ^2-test were used.

Results

Eight of the 48 women (four in each group) had ovulated at the time of laparoscopy or had not responded to the treatment as assessed by the absence of follicles >15 mm. Therefore, follicle aspiration was attempted in 20 women in each group (Table 1). No significant difference in the number of follicles (>15 mm) aspirated and the eggs recovered was found between the two groups. The recovery rate was 78% in the controls and 82% in the RU 486 treated women. Also, the number of eggs which fertilized *in vitro* (appearance of two pronuclei and subsequent cleavage) did not differ significantly between the two groups (fertilization rate 66% and 56% respectively). The same was found when only the oocytes recovered from the leading follicles (the largest) were assessed (15 from the controls and 16 from the RU 486 group, fertilization rate 73% and 68% respectively).

All embryos were examined in detail and graded on a scale of 0–10 according to recommended morphological criteria (Mohr & Trounson 1984). These criteria include the shape and number (even or uneven) of blastomeres, the rate of cleavage and the presence of fragments and of cytoplasmic granules (Watt *et al.* 1987) No significant difference in mean embryo score was found between the RU 486 group (mean 5·7, SD 2·5) and the controls (mean 5·5, SD 2·9).

Table 2 shows the mean (SE) levels of E2, progesterone and androstenedione in the follicular fluid of the leading follicle. No significant difference in the mean levels of these hormones was found between the RU 486 treated women (927, SE 93 ng/ml; 12 695, SE 1441 ng/ml and 179, SE 55 ng/ml respectively) and the controls (1120, SE 138 ng/ml; 12 630, SE 855 ng/ml and 119, SE 30 ng/ml respectively). Mean serum cortisol levels 12 h after administration of RU 486, i.e. 11 h after hCG injection, were significantly higher in the RU 486 group (562, SE 21 nmol/l) than in the control group (412, SE 27 nmol/l) (P<0·001, n=20).

The mean duration of the luteal phase, calculated from the day of laparoscopy to the day of the next menstrual period, did not differ significantly between the RU 486 (13·9, SE 0·4 days) and the control groups (13·6, SE 0·4 days). All cleaved oocytes in the present study were fixed at the four to eight cells stage for karyotyping as described previously (Watt *et al.* 1987).

Discussion

The results show that RU 486 at the dose used in the present study did not affect the in-vitro fertilization and cleavage of human oocytes. Since micromolar quantities of the compound were detected in the follicular fluid in all cases in which it was given (data not shown), the present results suggest that intrafollicular progesterone during the pre-ovulatory phase is not important for the final stages of human oocyte maturation. A previous study has shown that in sheep the oocyte should remain in the follicle for at least 6–8 h after the hCG injection in order to achieve normal fertilization *in vitro* (Trounson 1982). However, human oocytes can be fertilized *in vitro* even if they are recovered before in-vivo exposure to the mid-cycle LH activity (Templeton *et al.* 1986) and therefore to the pre-ovulatory progesterone rise. Thus, it appears that if progesterone plays a role in the maturation of human oocytes, this happens before the onset of the endogenous LH surge or the administration of hCG. At that time, progesterone is measured in substantial concentrations in the follicular fluid (Templeton 1985).

Table 2. Oestradiol, progesterone and androstenedione levels in the follicular fluid of the largest follicle in women treated with RU 486

Patient group	Oestradiol (ng/ml)	Progesterone (ng/ml)	Androstenedione (ng/ml)
Ru 486-treated (n=20)	927 (93)	12 695 (1441)	179 (55)
Control (untreated) (n=20)	1120 (138)	12 630 (855)	119 (30)

Results are means (SE) values.

In the present study, the developmental capacity of the oocytes after fertilization *in vitro* could not be fully determined, since the cleaving embryos were not replaced in a recipient uterus, and all embryos were fixed for karyotyping at the four to eight cells stage. However, the in-vivo exposure of the oocytes to the RU 486 did not influence their morphological characteristics after in-vitro fertilization. Although the grading score of the embryos was not very high, the fixed treatment schedule used in this study is believed to be optimal, since in an ET programme using a fixed regimen similar to that described here, a pregnancy rate of 20% per treatment cycle was achieved (Frydman *et al.* 1986).

Recent evidence has shown that RU 486 is not only a progesterone antagonist at the receptor level, but also has a direct suppressing effect on progesterone production by human granulosa cells *in vitro* (Dimattina *et al.* 1986). This effect seems to be mediated at least in part through inhibition of ovarian 3β-hydroxysteroid dehydrogenase activity in a dose-dependent manner (Dimattina *et al.* 1986). Our finding that follicular fluid progesterone levels were similar in the two groups suggests that either a higher dose of RU 486 would be needed to suppress progesterone production *in vivo* or that RU 486 fails to suppress progesterone biosynthesis in the presence of increasing follicular LH activity after the hCG injection.

Previous studies have shown the induction of menses or the termination of early pregnancy in women by the administration of RU 486 (Herrmann *et al.* 1982; Kovacs *et al.* 1984). But the failure of this compound to affect the in-vitro fertilization of pre-ovulatory human oocytes and its ability to block the mid-cycle gonadotrophin surge in monkeys and extend the menstrual cycle (Collins & Hodgen 1986) diminish the possibility of its use as a once-a-month contraceptive drug. In the present study, RU 486 did not produce any significant side-effects, and although there was a slight but significant rise in cortisol levels

12 h after the administration of the drug compared to controls, the duration of the luteal phase was not affected.

In conclusion, this study shows that RU 486 given to normal women at a single dose before the mid-cycle hCG administration was not able to affect the in-vitro fertilization of the oocytes. This provides evidence that progesterone is not critical for the maturation of human oocytes during the pre-ovulatory period.

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References

Botero-Ruitz, W , Laufer, N., DeCherney, A. H., Haseltine, F. P. & Behrman, H. R. (1984) The relationship between follicular fluid steroid concentration and successful fertilization of human oocytes in vitro. *Fertil Steril* **41,** 820-826.

Carson, R. S., Trounson, A. O. & Findlay, J. K. (1982) Successful fertilization of human oocytes *in vitro:* concentration of estradiol-17β, progesterone and androstenedione in the antral fluid of donor follicles. *J Clin Endocrinol Metab* **55,** 798-800.

Collins, R. L. & Hodgen, G. D. (1986) Blockade of the spontaneous midcycle gonadotrophin surge by RU 486: A progesterone antagonist or agonist? *J Clin Endocrinol Metab* **63,** 1270-1276.

Dimattina, M., Albertson, B., Seyler, D. E., Loriaux, D. L. & Falk, R. J. (1986) Effect of the antiprogestin RU 486 on progesterone production by cultured human granulosa cells: Inhibition of the ovarian 3β-hydroxysteroid dehydrogenase. *Contraception* **34,** 199-206.

Fishel, S. B., Edwards, R. G. & Walters, D. E. (1983) Follicular steroids as a prognosticator of successful fertilization of human oocytes *in vitro. J Endocr* **99,** 335-344

Frydman, R., Forman, R., Rainhorn, J.-D., Belaisch-Allart, J., Hazout, A. & Testart, J. (1986) A new approach to follicular stimulation for in vitro fertilization: programmed oocyte retrieval. *Fertil Steril* **46,** 657-662.

Healy, D. L , Baulieu, E E. & Hodgen, G. D (1983) Induction of menstruation by an antiprogesterone steroid (RU 486) in primates: site of action, dose-response relationships, and hormonal effects. *Fertil Steril* **40,** 253-257.

Herrmann, W., Wyss, R., Riondel, A., Philibert, D., Teutsch, G., Sakiz, E. & Baulieu, E. E. (1982) The effects of an antiprogesterone steroid on women: interruption of the menstrual cycle and of early pregnancy. *C R Seances Acad Sci (III)* **294,** 933-938.

Hillier, S. G., Wickings, E. J., Afnan, M., Margara, R. A., Harlow, C. R. & Winston, R. M L (1985) Intrafollicular sex steroids and oocyte function. In *Gamete Quality and Fertility Regulation* (Rolland, R., Heineman, M. J., Hillier, S. G. & Vemer, H., eds), Excerpta Medica, Amsterdam, pp. 43-52.

Kovacs, L., Sas, M., Besch, B. A., Ugocsai, G., Swahn, M. L., Bygdeman, M. & Rowe, P J. (1984) Termination of early pregnancy by RU 486—an antiprogestational compound. *Contraception* **29,** 399-410.

Messinis, I. E., Templeton, A., Angell, R. & Aitken, J. (1986) A comparison of fixed regimens for obtaining human cleaving oocytes for research purposes. *Br J Obstet Gynaecol* **93,** 39-42.

Mohr, L. & Trounson, A. (1984) In vitro fertilization and embryo growth. In *Clinical In Vitro Fertilization* (Wood, C. & Trounson, A., eds), Springer-Verlag, Berlin, pp. 99-115.

Templeton, A. A. (1985) Ovulation timing and IVF. In *In Vitro Fertilization and Donor Insemination* (Thompson, W., Joyce, D N. & Newton, J R., eds), Royal College of Obstetricians and Gynaecologists, London, pp. 45-59.

Templeton, A. A., Van Look, P., Lumsden, M. A., Angell, R , Aitken, J., Duncan, A. W. & Baird, D. T. (1984) The recovery of preovulatory oocytes using a fixed schedule of ovulation induction and follicle aspiration. *Br J Obstet Gynaecol* **91,** 148-154.

Templeton, A A , Van Look, P., Angell, R. E., Aitken, R. J., Lumsden, M. A. & Baird, D. T. (1986) Oocyte recovery and fertilization rates in women at various times after the administration of hCG. *J Reprod Fertil* **76,** 771-778

Trounson, A. (1982) In vitro fertilization. In *Topics in Experimental Endocrinology* (Martini, L. & James, V., eds), Academic Press, New York, pp. 43-73.

Uehara, S., Naganuma, T., Tsuiki, A., Kyono, K., Hoshiai, H. & Suzuki, M. (1985) Relationship between follicular fluid steroid concentrations and in vitro fertilization. *Obstet Gynecol* **66,** 19-23.

Watt, J. L., Templeton, A. A., Messinis, I., Bell, L., Cunningham, P. & Duncan, R. (1987) Trisomy 1 in an eight cell human pre-embryo. *J Med Genet* **24,** 60-64.

Wramsby, H., Kullander, S., Liedholm, P., Rannevik, G., Sundstrom, P. & Thorell, J. (1981) The success rate of in vitro fertilization of human oocytes in relation to the concentrations of different hormones in follicular fluid and peripheral plasma. *Fertil Steril* **36,** 448-454

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The effect of epostane, a 3-beta hydroxy steroid dehydrogenase inhibitor, on maternal and fetal steroid levels during mid-gestation

MARK SELINGER, IAN Z. MACKENZIE, MICHAEL D. GILLMER,
SUE L. PHIPPS, JANE FERGUSON

Summary. A double-blind, placebo-controlled trial was conducted to assess the maternal and fetal endocrine effects of epostane, an inhibitor of progesterone synthesis, in mid-pregnancy. Although present in the maternal circulation, epostane was not detected in cord blood or amniotic fluid. Maternal and fetal progesterone levels fell by 80% and 95% respectively with maintenance of the fetal arterio-venous difference while oestradiol and aldosterone levels were affected to a lesser extent. The mechanism of 3-beta hydroxy steroid dehydrogenase suppression and the relation between fetal and maternal progesterone levels are discussed.

Epostane (4,5 epoxy-17 hydroxy-4,17 dimethyl 3 oxo androstane-2 carbonitrile, WIN 32,729, Sterling Winthrop [SWRD], Guildford, Surrey) is a synthetic steroid which inhibits steroid synthesis *in vivo* by competitive inhibition of the 3β-hydroxy steroid dehydrogenase delta 4-5 isomerase enzyme system (3-beta HSD), resulting in decreased production of progesterone and an increase in its biologically inactive precursor pregnenolone (van der Spuy *et al.* 1983). In pregnant women this results in a reduction in circulating progesterone levels in the first (Pattison *et al.* 1985*a*, *b*) and second trimesters (Selinger *et al.* 1987) indicating an inhibition of both luteal and placental/decidual progesterone synthesis. The physiological effects of this in mid-pregnancy include increased sensitivity to endogenous and exogenous oxytocic agents resulting in significantly reduced induction–abortion intervals (Selinger *et al.* 1987). It is postulated that a similar effect will occur in the third trimester thereby improving induced labour outcome. The aim of this pilot study was to assess placental transfer of epostane and its effects on maternal and fetal steroid levels.

Patients and methods

The double-blind, placebo-controlled trial included 10 women at 16–20 weeks gestation who were scheduled to have a prostaglandin-induced termination of pregnancy within the terms of the 1967 Abortion Act. All the women gave informed consent and local ethics committee approval for the trial was sought. The menstrual dates were confirmed with ultrasonography and patients were randomly allocated to be given a bottle containing either nine 100-mg tablets of epostane (epostane group) or nine identical placebo tablets (placebo group); one tablet was to be taken on waking, one at 14.00 hours and one on going to bed, for the 72 h preceding the planned induction of abortion. The last tablet was to be taken on the morning of admission to hospital. Drug allocation was randomized by number, the code being held by SWRD Alnwick, Northumberland.

Nuffield Department of Obstetrics and Gynaecology, John Radcliffe Hospital, Headington, Oxford
MARK SELINGER *Research Fellow*
IAN Z. MACKENZIE *Reader and Honorary Consultant*
MICHAEL D. GILLMER *Consultant Gynaecologist*
SUE L. PHIPPS *Medical Laboratory Scientific Officer*
JANE FERGUSON *Research Sister*

Correspondence: M. Selinger

Before treatment, a peripheral venous blood sample was taken (pretreatment sample) and a further sample was taken on admission to hospital 3–5 h after the last tablet had been taken immediately before fetoscopy (post-treatment sample), which was carried out under 5–10 mg diazepam sedation using the technique described by MacKenzie & MacLean (1980). The pre- and post-treatment samples were all taken between 09.00 and 14.00 hours. Fetal artery and vein blood was aspirated from the umbilical vessels into EDTA, heparinized and plain bottles, and an aliquot of amniotic fluid was taken from each patient: the vessel of origin was confirmed using blood gas analysis. Following fetal blood sampling 5 mg of prostaglandin (PG) E_2 (Upjohn) was injected into the amniotic cavity and the abortion was managed in the usual way. Following abortion of the fetus but before surgical evacuation of the uterus, when necessary, a final maternal venous sample was collected (post-abortion sample).

All the maternal blood samples were analysed for haematological (Hb, WBC, platelets, group), hormonal (progesterone, oestradiol, aldosterone, cortisol, hCG), biochemical (Na^+, K^+, Cl^-, HCO_3^-, urea, creatinine, albumin, AST, gamma-glutamyl TP, alkaline phosphatase) and epostane levels. Progesterone, oestradiol and cortisol levels were assayed using a technique described by Turnbull *et al.* (1974), aldosterone levels were assayed using a commercial radioimmunoassay kit supplied by Serono, Diagnostics, Woking, Surrey, UK. Serum samples were stored at −20°C until the study had been completed. Each steroid assay was carried out as a single run. Fetal blood samples were analysed for progesterone, oestradiol, epostane, and, where quantity permitted, aldosterone, hCG and cortisol levels. Epostane levels were measured using high-pressure liquid chromatography by SWRD, Alnwick, Northumberland. The minimum quantifiable levels of epostane were 75 ng/ml in amniotic fluid and 50 ng/ml in serum samples with an average intra-assay precision ±12% for each run.

Before and after taking the tablets the patients were asked specific questions about uterine pain, vaginal bleeding, threatened or spontaneous miscarriage and any symptoms that could have been due to side-effects or drug reactions. The answers were recorded on each treatment protocol by one author (M.S.).

Results

Table 1 gives the patient details for the epostane and placebo groups. There were no statistically significant differences in these details between the two groups (Mann–Whitney *U*-test). No drug reactions or side-effects were recorded during the treatment period before admission to hospital, and uterine pain, vaginal bleeding and miscarriage did not occur in any patient before admission to hospital. There were no drop-outs from the study.

Maternal steroid levels

Table 2 lists the maternal steroid levels at the three sampling times for the two groups. The mean post-treatment and post-abortion progesterone levels in the epostane group were significantly lower than in the placebo group ($P<0·01$ and $P<0·05$ respectively: Wilcoxon's two-sample test). Within-group analyses showed a significant fall in mean progesterone levels in the epostane group between the pre- and post-treatment samples ($P<0·01$, Student's *t*-test) which was not found in the placebo group. Mean progesterone levels post-abortion were significantly lower than pretreatment values in both groups ($P<0·01$, paired *t*-test)

Oestradiol concentrations fell significantly after 72 h treatment in the epostane group but not in the placebo group ($P<0·05$, Student's *t*-test), although post-abortion values were significantly lower than pretreatment values in both groups ($P<0·005$, paired *t*-test).

Mean cortisol and aldosterone levels were not significantly different between the epostane and placebo groups at any of the three sampling times nor were the haematological, biochemical or hepatic enzyme indices measured.

Table 1. Characteristics of patients in the two treatment groups

Variable	Epostane (n = 5)	Placebo (n = 5)
Age (years)	23·1 (3·2)	22·9 (7·8)
Height (cm)	160·0 (5·1)	161·0 (4·8)
Weight (kg)	62·8 (4·6)	60·5 (9·5)
Gestation (weeks)	17·4 (1·9)	16·1 (1·2)

Results are means (SD).

Table 2. Maternal peripheral venous serum steroid levels at three sampling times in the groups treated with epostane or placebo

Steroid	Group	Sampling time		
		Pretreatment	Post-treatment	Post-abortion
Progesterone (ng/ml)	Epostane	46·1 (21·1)	5·0 (2·2)	2·6 (1·5)
	Placebo	27·5 (6·1)	28·4 (5·3)	5·7 (3·4)
Oestradiol (nmol/l)	Epostane	17·4 (11·5)	1·6 (0·8)	0·8 (0·6)
	Placebo	13·1 (9·1)	11·5 (6·6)	0·5 (0·2)
Cortisol (nmol/l)	Epostane	627 (332)	433 (211)	456 (128)
	Placebo	506 (183)	347 (107)	504 (287)
Aldosterone (pg/ml)	Epostane	267 (199)	<30 —	191 (116)
	Placebo	274 (75)	65 (44)	265 (141)

<30 below minimum accurately quantifiable amount.
Results are means (SD); there were five subjects in each group.

Fetal steroid levels

Table 3 gives the mean serum steroid levels in maternal venous (post-treatment sample) and in umbilical artery and vein blood in the two groups together with the progesterone level in each sample assayed. Progesterone levels were always higher in the fetal than the maternal circulation in both groups. Similarly, in each patient progesterone levels were always higher in umbilical vein than in umbilical artery. Figure 1 shows the relation between the fetal and maternal progesterone, aldosterone and oestradiol levels in each woman at fetoscopy. Progesterone levels in both fetal vessels were significantly lower in the epostane group than in the placebo group ($P<0·01$ for both vessels; Mann–Whitney *U*-test). There was no consistent relation between fetal artery and vein oestradiol levels in either group and there appeared to be no consistent relation between the maternal and fetal oestradiol levels. There was no statistically sig-

Table 3. Progesterone, oestradiol and aldosterone levels in umbilical vein and artery and maternal vein blood samples after treatment with epostane or placebo

Steroid	Group	*n*	Umbilical		Maternal vein (post-treatment)
			Vein	Artery	
Progesterone (ng/ml)	Epostane	1	15·50	10·12	8·30
		1	10·95	5·28	3·10
		1	—	14·11	6·20
		1	14·94	10·67	3·10
		1	10·32	4·66	4·40
		mean (SD)	12·9 (2·6)	8·9 (3·9)	5·0 (2·2)
	Placebo	1	—	551·90	31·40
		1	165·90	90·22	30·50
		1	128·87	81·46	24·00
		1	180·96	120·87	36·00
		1	301·09	198·78	21·50
		mean (SD)	194·2 (74)	208·6 (197)	28·4 (5·3)
Oestradiol (nM/l)	Epostane	4	2·3 (1·1)	1·7 (0·9)	1·6 (0·8)
	Placebo	4	5·8 (3·8)	6·5 (7·9)	11·4 (6·5)
Aldosterone (pg/ml)	Epostane	3	253 (121)	173 (16)	<30 —
	Placebo	4	217 (39)	246 (11)	65·4 (44)

Results are means (SD) where appropriate; progesterone levels are also shown for individual patients
— denotes missing values

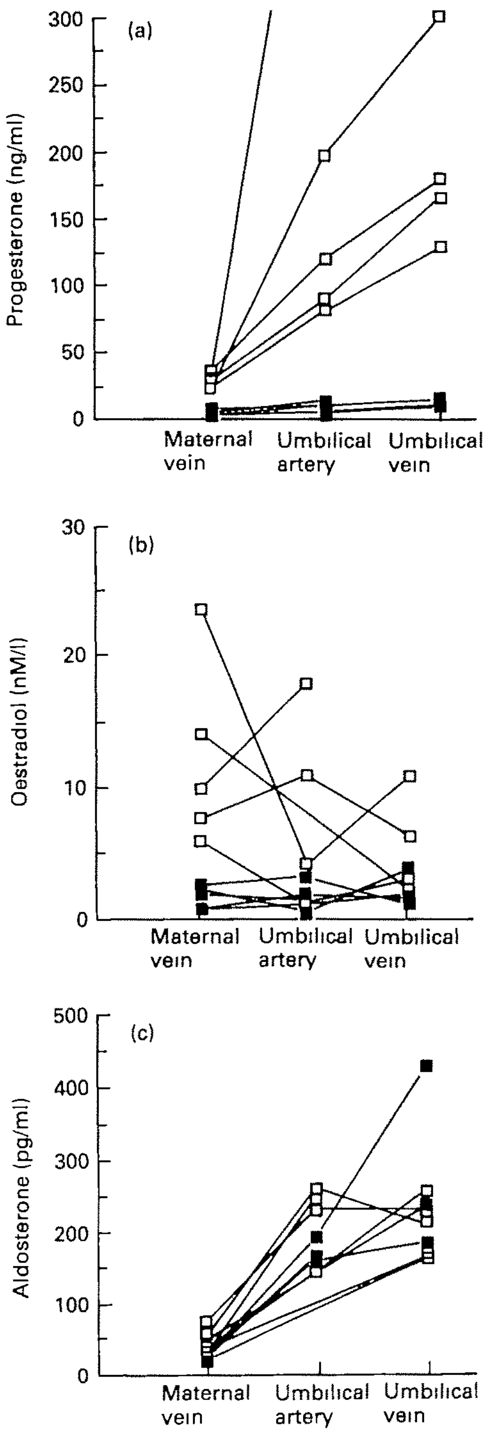

Fig. 1. Progesterone (a), oestradiol (b) and aldosterone (c) levels in paired maternal and fetal blood samples obtained at fetoscopy in five women after treatment with epostane (■) and in five others treated with placebo (□).

nificant difference between fetal umbilical artery and vein aldosterone levels within each of the groups. There was no difference in umbilical vein aldosterone levels between the two groups but umbilical artery aldosterone levels were higher in the placebo group than in the epostane group ($P<0{\cdot}01$, Mann–Whitney *U*-test).

Epostane levels

Epostane was not detected in any of the samples from the placebo group. Epostane was detected in all maternal serum samples from the epostane group 72 h after starting oral treatment, with levels varying from 390 to 823 ng/ml. The time in minutes between taking the last tablet of epostane and the post-treatment blood sample varied from 65 min to 350 min. Epostane was not detected in any amniotic fluid or umbilical blood samples.

Discussion

It is thought that the effect of epostane on myometrial contractility depends on the inhibition of placental and/or decidual synthesis of progesterone (Lopez-Bernal *et al.* 1986) releasing the myometrium from the progesterone 'block' (Csapo 1973) and sensitizing it to endogenous and exogenous prostaglandins (Webster *et al.* 1985*a*, *b*; Selinger *et al.* 1987).

Epostane was detectable in all the maternal samples after treatment with epostane and in none of the placebo group, and although the assay was hindered in one case by a confounding peak on the high-pressure liquid chromatography results these data confirm that the medication was taken by all the treatment group.

There was a wide variation in the levels of epostane from 320 to 890 ng/ml but there was no correlation with the time interval between ingestion of the last tablet and post-treatment sampling nor was there any correlation between the epostane and progesterone levels in each patient. Epostane was not detectable in any of the fetal sera or amniotic fluid samples. These data suggest that either the fetal level of epostane was below the detectable minimum or that the drug did not cross the placenta into the fetal circulation. Previous drug kinetic studies have shown a feto-maternal distribution ratio of 1:3 for PGE_2 (B. M. Castle, unpublished data), and mefenamic acid (MacKenzie *et al.* 1985). The epostane molecule is similar to progesterone in structure and size and it is believed that steroid molecules move freely between the maternal and fetal circulations. Our data cannot exclude the possibility that epostane entered the fetal compartment and became bound to the placental 3-beta HSD enzyme system. However, the changes in fetal steroid levels discussed below could all have been secondary to the changes in the maternal levels and not due to inhibition of fetal 3-beta HSD.

The 89% reduction of maternal progesterone levels after treatment with epostane is in agreement with previous studies (Webster *et al.* 1985*a,b*; Selinger *et al.* 1987). The present results also indicate that epostane causes a fall in circulating progesterone levels in the fetus which mirror the maternal changes.

There are no standard data for mid-trimester umbilical vein progesterone levels. Tulchinsky & Okada (1975) reported feto-maternal progesterone ratios of 14:1 in umbilical and maternal vein blood samples in full-term infants at birth. We found feto-maternal progesterone ratios in vein blood of 3·0–9·7:1 in the placebo group. Similarly, in the epostane-treated group, there was a consistent linear relation between maternal and umbilical vein progesterone levels with a correlation coefficient of 0·931 ($n = 5$, $P<0{\cdot}001$). It is believed that the placenta at term secretes 90% of its 250–350 mg/day output of progesterone into the maternal circulation and 10% into the fetal circulation (Tulchinsky & Okada 1975). The higher concentrations found in the fetal circulation can be explained by difference in the blood volumes in the two circulations. The explanation for the smaller difference in ratio in the second trimester questions this theory. It could, however, result from the differing experimental method of Tulchinsky & Okada (1975), or reflect the endocrine changes surrounding parturition. It is also possible that the proportion of progesterone secreted into the fetal circulation changes with gestation or that free feto-maternal exchange of progesterone does not take place throughout the pregnancy and itself may be one of the endocrine changes surrounding the onset of labour. If feto-maternal exchange remains constant during pregnancy the data from this study could also represent inhibition of decidual progesterone synthesis and compensatory efflux of progesterone from the fetal circulation without direct inhibition of placental 3-beta HSD activity.

The consistent venous-arterial (v-a) gradient in fetal progesterone levels provides further support for this theory. The v-a difference suggests that the fetus 'consumes' progesterone, using it either as a precursor for other steroid molecule syntheses, biotransforming it in the fetal liver before excretion or using it as an energy source. Pregnanediol, the progesterone metabolism byproduct, was not measured in this study due to the small amount of fetal serum available for analysis in each case but its quantitation could indicate the fate of progesterone arriving at the fetus via the umbilical vein.

Maternal oestradiol concentrations were also affected by epostane with levels falling by an average of 91% following treatment with epostane and although levels of oestradiol tended to be lower in the fetal blood samples taken from the epostane group, the materno-fetal differences were not statistically significant. In the placebo group umbilical oestradiol levels were, however, consistently lower than the maternal levels. The observation on maternal oestradiol concentration changes is at variance with the lack of effect of epostane on maternal oestradiol levels previously reported (Selinger *et al.* 1987), although similar decreases in concentration have been recorded in the first trimester (Webster *et al.* 1985*a,b*). We did not observe any consistent effect on cortisol or aldosterone levels in either maternal or fetal circulations after treatment with epostane.

These data confirm that epostane inhibits the 3-beta HSD enzyme system causing profound changes in both maternal and fetal progesterone levels and lesser changes in the other steroid concentrations measured. It remains unclear whether the fetal steroid effects are secondary to maternal concentration changes or a direct effect of epostane on placental enzyme systems. Epostane has now been withdrawn for commercial reasons, but further research is required to confirm these data and attempt to separate the activities of the placental and decidual 3-beta HSD systems in other similar drugs.

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References

Csapo, A. I., Pulkinnen, M. O. & Kaihola, H. L (1973) The effect of lute-ectomy induced progesterone withdrawal on the oxytocin response of the first trimester pregnant human uterus. *Prostaglandins* **4,** 421-429.

Lopez-Bernal, A., Tindell, D J , Selinger, M. & Turnbull, A. C. (1986) Inhibition of progesterone production in human chorio-decidua by Epostane. *Horm Metab Res* **7,** 503

MacKenzie, I Z. & MacLean, D. A. (1980) Pure fetal blood from the umbilical cord at fetoscopy: experience of 125 consecutive cases. *Am J Obstet Gynecol* **138,** 1213-1218.

MacKenzie, I Z., Graf, A. K. & Mitchell, M. D. (1985) Prostaglandins in the fetal circulation following maternal ingestion of a prostaglandin synthesase inhibitor during mid-pregnancy. *Int J Gynecol Obstet* **23,** 455-458.

Pattison, N. S., Webster, A. M., Phipps, S. L., Anderson, A. B. M. & Gillmer, M D. (1985*a*) Inhibition of 3-beta hydroxy steroid dehydrogenase activity in first and second trimester human pregnancy and the luteal phase using epostane *Fertil Steril* **42,** 875-881

Pattison, N. S., Webster, A. M., Phipps, S. L., Anderson, A. B. M. & Gillmer, M. D. (1985*b*) Prolonged inhibition of placental and ovarian 3 hydroxysteroid dehydrogenase during pregnancy and the luteal phase of the menstrual cycle. *J Obstet Gynaecol* **5,** 69-74.

Selinger, M., MacKenzie, I Z., Gillmer, M. D , Phipps, S. L. & Ferguson, J. (1987) Progesterone inhibition in mid-trimester termination of pregnancy: physiological and clinical effects. *Br J Obstet Gynaecol* **94,** 1218-1222.

Tulchinsky, D. & Okada, D. M. (1975) Hormones in human pregnancy. IV. Plasma progesterone. *Am J Obstet Gynecol* **121,** 293-295.

Turnbull, A. C., Flint, A. P. F., Jeremy, J. Y., Patten, P. T., Kierse, M. J. M. C. & Andersen, A. B M. (1974) Significant fall in progesterone and rise in estradiol levels in human peripheral plasma before onset of labour. *Lancet* **i,** 101-103.

van der Spuy, S , Jones, D L., Wright, C. S W., Piura, B., Paintin, D. B., James, V. H. T. & Jacobs, H. S. (1983) Inhibition of 3-beta hydroxysteroid dehydrogenase activity in first trimester human pregnancy with Trilostane and WIN 32,729. *Clin Endocrinol* **19,** 521-531.

Webster, M. A., Pattison, N. S., Phipps, S. L. & Gillmer, M. D. (1985*a*) Myometrial activity in first trimester human pregnancy after Epostane therapy. Effect of intravenous oxytocin. *Br J Obstet Gynaecol* **92,** 957-962

Webster, M. A., Phipps, S. L. & Gillmer, M D. (1985*b*) Interruption of first trimester human pregnancy following Epostane therapy. Effect of prostaglandin E_2 pessaries. *Br J Obstet Gynaecol* **92,** 963-968.

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The effect of pelvic floor exercises in the treatment of genuine urinary stress incontinence in women at two hospitals

S. M. HENALLA, P. KIRWAN, C. M. CASTLEDEN, C. J. HUTCHINS, A. J. BREESON

Summary. The results of the pelvic floor exercises for the treatment of genuine stress incontinence of urine were compared between two different hospitals geographically 50 miles apart. A perineal pad weighing test was used to assess the quantity of urine lost during exercise before and after treatment. A similar percentage of patients in the two studies responded to treatment and became either completely dry or significantly improved at the end of 3 months interval; 69% at LCH and 65% at LGH. Overall, 67% of patients achieved complete continence or a significant improvement as a result of pelvic floor exercises alone.

Stress urinary incontinence is the commonest form of female incontinence. Treatment has varied between conservative management with various forms of physiotherapy (Brown 1977) to a variety of surgical procedures (Stanton & Cardozo 1979). Previous reports have shown different success rates for treatment of stress urinary incontinence by pelvic floor exercises since Kegel (1951) introduced this idea. It is widely believed among clinicians that various forms of physiotherapy are useful in treatment for genuine stress incontinence in selected patients (Wilson 1984). However, Jones (1963) suggested that the majority of women achieve continence when pelvic floor exercises alone were the primary treatment. Montgomery & Shepherd (1983) and Harrison (1983) noted that success following pelvic floor exercises depended on the instructor's enthusiasm and knowledge and on the patient's co-operation and motivation. In some series good results were achieved after 4 weeks of treatment with pelvic floor exercises (Castleden *et al.* 1984).

The aim of the present study was to assess, by objective means, the value of pelvic floor exercises in the treatment of urinary stress incontinence. We have compared the results in the two different hospitals from patients who were treated by two different physiotherapists in order to assess the reproducibility of such treatment. The perineal pad weighing technique was used to assess the severity of the condition and the response to the treatment provided. This was originally described by Caldwell (1974) and subsequently tested by Sutherst *et al.* (1981). Its reproducibility has been assessed by Christensen *et al.* (1984) and Mundt-Petterssen *et al.* (1984). A slight modification of this technique was used

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Leicester General Hospital, Leicester LE5 4PW
Department of Obstetrics and Gynaecology
S. M. HENALLA *Lecturer*
P. KIRWAN *Senior Lecturer*

Department of Geriatrics
C. M. CASTLEDEN *Professor*

Department of Obstetrics and Gynaecology, George Eliot Hospital, Nuneaton
C. J. HUTCHINS *Consultant*

Department of Obstetrics and Gynaecology, Lincoln County Hospital, Lincoln
A. J. BREESON *Consultant*

Correspondence: Mr S. M. Henalla, Senior Registrar, Department of Obstetrics and Gynaecology, The Jessop Hospital for Women, Leavygreave Road, Sheffield S3 7RE

in the present study and its reproducibility has been assessed (Fig. 1).

Patients and methods

The two studies were conducted at Lincoln County and Leicester General Hospitals. The first study conducted at Lincoln County Hospital was in the form of a pilot study. Forty-nine consecutive women with incontinence problems were considered. Five were lost to follow-up and 12 had detrusor instability, the other 32 patients had urodynamically proven genuine stress incontinence. They had a mean age of 46 years (range 27–77 years) and entered our first study. The second study was conducted at Leicester General Hospital. This was a randomized controlled study which included 104 patients. These patients were allocated at random to four different groups. The first group of 26 patients received a course of pelvic floor exercises for 3 months. The results of treatment in this group were compared with the results obtained in the first study. The other three groups form a part of another randomized controlled study and are not considered in this paper.

Patients who entered the two studies had the same routine filling and voiding cystometry, urethral pressure studies as well as fluid bridge test before their enrolment in these two studies. All these patients had a normal detrusor pressure profile at rest and on stress. Perineal pad weighing test was performed to quantify the amount of urine loss during defined domestic

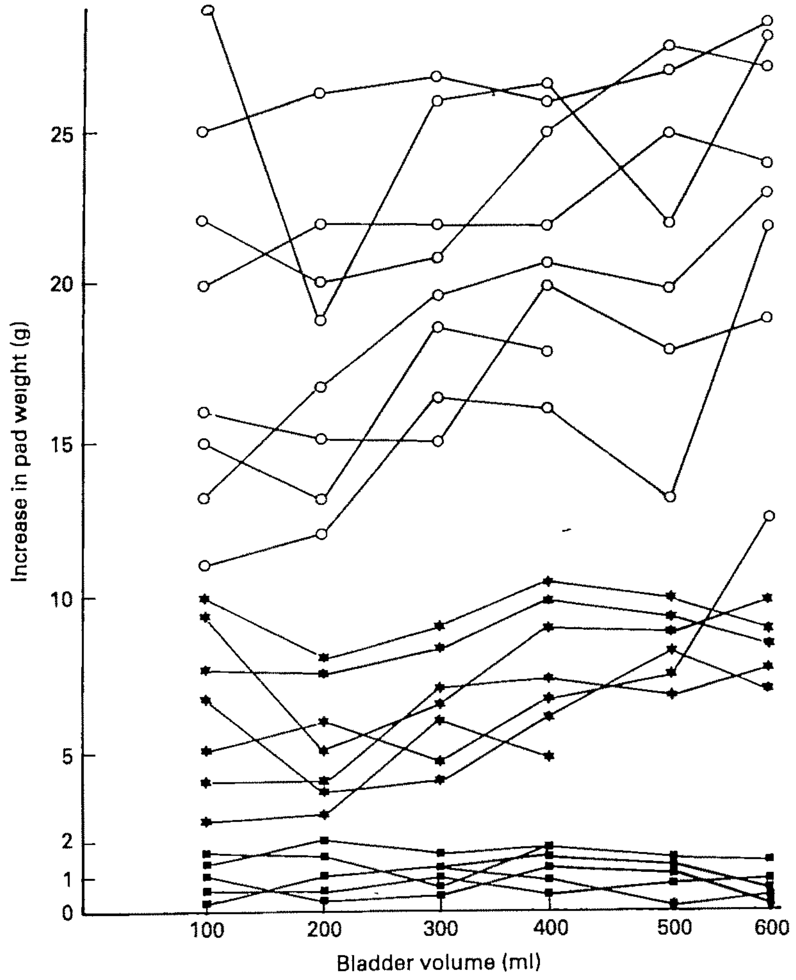

Fig. 1. Reproducibility of pad weighing test in 20 patients complaining of urinary stress incontinence: ■, mild; ✱, moderate; ○, severe.

Table 1. Exercise programme for pad testing

1. Washing hands × 10 times
2. Walking around the ward for 5 min
3. Picking up objects × 10 times
4. Lifting two sandbags 8lb each × 10 times
5. Squatting × 10 times
6. Climbing up stairs × 2 times (two floors)
7. Stretching abdominal muscles × 10 times
8. Jumping up and down × 10 times
9. Jumping and coughing × 10 times
10. Coughing while pushing down × 10 times

and stressful exercises (Table 1). Patients were asked not to pass urine from 4 h before test, as it has been shown previously that bladder volume has only a small influence on the amount of urine loss (Sutherst *et al.* 1984). The exercise programme which was used was accepted by all patients. Each pad was weighed before and after exercise to determine the amount of urine loss, and the urine volume passed on completion of the programme was measured. The degree of stress incontinence was graded as mild (urine loss at all exercises <2 ml), moderate (maximum urine loss at one exercise 2–10 ml) and severe (urine loss >10 ml). The 32 patients in the first study and the 26 patients in the second study were seen by two different physiotherapists in the two different hospitals but they were assessed by the same investigator. The two groups of patients were comparable regarding their age, weight, parity, and the severity of incontinence (Table 2). After a simple description of the pelvic floor muscles, the physiotherapist taught the patient to contract the correct muscles. This was achieved by asking the patient to insert into her vagina the index and middle fingers of her right hand. Both fast and slow types of contractions were practised. The fast contractions were performed in time as the patient said: contract-relax, contract-relax. The slow contractions were sustained for between 3 and 4 s, with the patient counting up to 5. Equal numbers of fast and slow contractions were performed in each session. The frequency of the exercise sessions was increased gradually until they were performed hourly during the day. Each session lasted up to 10 min at any one time depending on the response of the patient to the exercise. The patients were supervised carefully by a particular physiotherapist with a special interest in incontinence in the relevant hospital. Both physiotherapists performed vaginal examinations, using the index and middle fingers, while the patient was lying on her back for weekly assessment.

Full clinical assessment and pad testing with the same volume of fluid as the initial test in the bladder were repeated after treatment was completed.

Results

Figures 2 and 3 show the pad weight changes after treatment with pelvic floor exercises at the two hospitals. The χ^2-test was used to assess the influence of age, the severity of the condition and the duration of symptoms on the response rate after pelvic floor exercise treatment in both studies (Table 3). Neither the severity of the condition nor the patient's age had a significant effect on the treatment results, but the treatment

Table 2. Age, weight, parity, and severity of incontinence in the two groups of patients treated with pelvic floor exercises at Lincoln County (LCH) and Leicester General Hospital (LGH)

Variables	LCH ($n = 32$)	LGH ($n = 26$)
Age (years)		
Range	27–77	26–74
Mean (SD)	46·2 (12·5)	45·9 (10·9)
Weight (kg)		
Range	51–102	50–81
Mean (SD)	66·1 (13·0)	65·2 (7·9)
Parity		
Range	0–4	1–6
Mean (SD)	2·2 (1·1)	2·8 (1·5)
Severity of incontinence		
Mild	8	8
Moderate	13	7
Severe	11	11

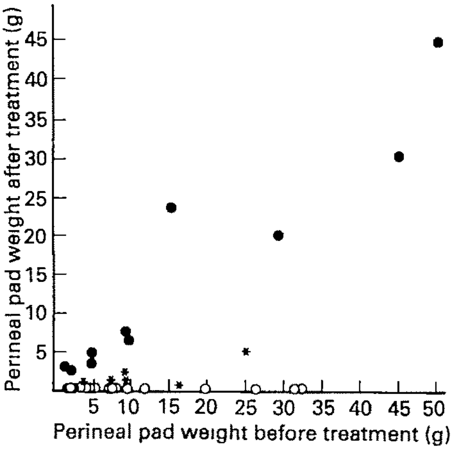

Fig. 2. Effects of exercise treatment on urine loss measured by perineal pad weighing test. O, cured; ✱, improved; ●, failed. (Lincoln County Hospital.)

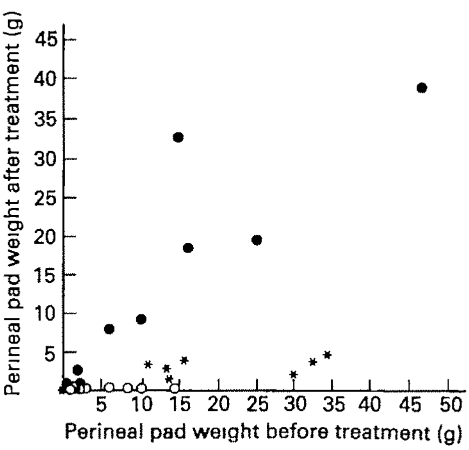

Fig. 3. Effects of exercise treatment on urine loss measured by perineal pad weighing test. O, cured; ✱, improved; ●, failed. (Leicester General Hospital.)

was more effective with a shorter duration of symptoms (<1 year) ($P<0{\cdot}05$). Similar results were obtained in the two studies. Table 3 shows a comparison between the duration of stress incontinence in the two groups of patients treated with pelvic floor exercises at the two hospitals.

Discussion

In the two studies we have attempted to assess objectively the effect of pelvic floor exercises for the treatment of pure stress incontinence. The pad weighing technique was used for grading the severity of incontinence as it is simple, inexpensive and proved to be fairly reproducible. We have tested the reproducibility and accuracy of our pad weighing technique with gradual increasing amounts of bladder volume in 20 patients with different grades of stress incontinence (Fig. 1). The two studies show that pelvic floor exercises are an effective conservative method for treating genuine stress incontinence of urine.

Overall, 58 patients with genuine stress incontinence were treated with pelvic floor re-edu-

Table 3. Effect of age, severity and duration of symptoms on response to treatment with pelvic floor exercises in patients with urinary incontinence at two hospitals

	Lincoln County Hospital		Leicester General Hospital	
Variable	Cured/improved ($n = 22$)	Unchanged ($n = 10$)	Cured/improved ($n = 17$)	Unchanged ($n = 9$)
Age (years)				
26–39	8	2	5	3
40–60	10	6	10	6
>60	4	2	2	—
Degree of incontinence				
Mild	6	2	5	3
Moderate	9	4	5	2
Severe	7	4	7	4
Duration of symptoms (years)				
<1	13*	2	8*	2
1–3	7	3	6	1
>3	2	5	3	6

The treatment was significantly more effective after the shortest duration of symptoms *$P<0{\cdot}05$ χ^2-test.

cation by a simple exercise regimen and 67% showed improvement or complete relief after 3 months. Similar results were achieved at the two hospitals (Figs 2 & 3) although two different physiotherapists were involved. Neither age nor the severity of the condition should influence the selection of patients for pelvic floor exercises. From Figs 2 and 3 it appears that there was a higher proportion with complete relief of incontinence at the District General Hospital (50%) than at the Central Regional Hospital (35%). This observation could not be explained by the patients' ages, weights, parity, severity of incontinence or previous history. However, this may be due to the difference between the two groups in the duration of their incontinence and the nature of their recruitment to both studies. A certain number of patients seen at Lincoln County Hospital were recruited via an advertisement on the local radio. This may explain why a larger percentage of these patients had a shorter duration of symptoms than those treated at the Leicester General Hospital. There is no associated morbidity with this method of treatment in comparison with surgery. The physiotherapist should be experienced in this particular field and should be able to examine the patient vaginally at each attendance to ensure that pelvic floor exercises are undertaken in the correct manner.

About one third of the patients in both studies failed to respond to physiotherapy. Some of these women did not perform the exercises conscientiously and were poor attenders and so may be considered patient rather than method failures. However, some women with stress incontinence are not helped by exercises and this is the group for whom surgery must be considered.

Acknowledgments

We thank all the consultant gynaecologists at Lincoln County, Leicester General Hospitals and Leicester Royal Infirmary for their co-operation by patient referrals. We also gratefully acknowledge the hard work of Mrs Taylor and Mrs Robinson at the physiotherapy departments in both hospitals at Lincoln and Leicester.

References

Brown, A. D B. (1977) Post-menopausal urinary problems. *Clin Obstet Gynaecol* **4**, 181-206.

Caldwell, K. P. S. (1974) Clinical use of a recording nappy *Urol Int* **29**, 172-173.

Castleden, C. M , Duffin, H. M. & Mitchell, E. P. (1984) The effect of physiotherapy on stress incontinence *Age Ageing* **13**, 235-237

Christensen, J., Colstrup, H , Hertz, J , Lenstrup, C. & Frimodt-Mollen (1984) Inter and intradepartmental variations of the urine pad weighing test. In *Proceedings of the 14th Annual Meeting of the International Continence Society,* Innsbruck, pp. 99-100.

Harrison, S. M. (1983) Stress incontinence and the physiotherapist. *Physiotherapy* **69**, 144-147.

Jones, E G. (1963) Nonoperative treatment of stress incontinence. *Clin Obstet Gynecol* **6**, 220-235.

Kegel, A H. (1951) Physiologic therapy of urinary incontinence. *JAMA* **146**, 915-918.

Montgomery, E. & Shepherd, A. N. (1983) Electrical stimulation and graded pelvic exercises for genuine stress incontinence. *Physiotherapy* **69**, 12.

Mundt-Petterssen, B., Mattleasson, A. & Sundin, T (1984) Reproducibility of the one hour incontinence test. In *Proceedings of the 14th Annual Meeting of the International Continence Society,* Innsbruck, pp. 90-91.

Stanton, S. L. & Cardozo, L. (1979) A comparison of vaginal and suprapubic surgery in the correction of incontinence due to urethral sphincter incompetence. *Br J Urol* **51**, 497-499.

Sutherst, J., Brown, M. & Shawer, M. (1981) Assessing the severity of urinary incontinence in women by weighing perineal pads. *Lancet* **i**, 1128-1130.

Sutherst, J , Malcolm, B. & Rishmond, D. (1984) Quantifying urine loss: studies on the exercise regimen. In *Proceedings of the 14th Annual Meeting of the International Continence Society,* Innsbruck, pp. 96-98.

Wilson, P. D (1984) The value of physiotherapy in female genuine stress incontinence. In *Proceedings of the 14th Annual Meeting of the International Continence Society,* Innsbruck, pp. 156-158.

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Detrusor instability following colposuspension for urinary stress incontinence

R. LANGER, R. RON-EL, M. NEWMAN, A. HERMAN, E. CASPI

Summary. Sixty-two patients with genuine stress incontinence (group A) and 30 women with combined detrusor instability and genuine stress incontinence (group B) had a colposuspension operation. The proportion with symptoms of detrusor instability was significantly reduced from 24% before operation to 9% after operation in group A and from 73% to 33% in group B. Urodynamically, detrusor instability developed after surgery in 17 of the 62 patients (27%) in group A whereas only 12 of the 30 women (40%) in group B had detrusor instability after surgery. No urodynamic explanation was found to explain the effect of colposuspension in relieving the symptoms of detrusor instability in some and causing them in others. Nevertheless, it is suggested that colposuspension is helpful for most patients with combined detrusor instability and genuine stress incontinence.

It is widely accepted that in most patients with genuine stress incontinence this can be cured by surgery. Most reports suggest that the cure rates achieved by a suprapubic approach are higher than those for vaginal surgery (Morgan 1973). The colposuspension operation first described by Burch (1961) has been shown to produce objective evidence of a cure in 89% of the patients (Stanton *et al.* 1976). The present study, using pre- and postoperative urodynamic assessment, investigates the outcome and occurrence of detrusor instability following colposuspension surgery for genuine urinary stress incontinence.

Patients and methods

From 1983 to 1985, 92 patients underwent a colposuspension operation for genuine urinary stress incontinence in our department. Before operation all patients had a gynaecological, urological and neurological examination. The urodynamic investigations included cystometry, uroflowmetry, urethral pressure profile, and voiding cystography. Cystometry and uroflowmetry were performed using the Lectromed Urinary Investigation System 5000. The urethral pressure profiles were obtained with the Gaeltec dual microtransducer. These investigations were repeated on all patients 3–6 months postoperatively. Frequency was defined as the passage of urine seven or more times during the day or twice or more at night and urgency as a strong desire to void. The methods, definitions and units conform to the International Continence Society (1981). Detrusor instability was subdivided according to Cardozo *et al.* (1979). The operation performed was the Burch colposuspension with modification suggested by Stanton & Cardozo (1979). The mean follow-up period was 19 months (range 6–39 months). The statistical methods used were McNemar's paired χ^2 test for comparing proportions relating to the same subjects and the χ^2 test for comparing proportions relating to subjects in different groups. Non-parametric methods were

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Department of Obstetrics and Gynecology, Assaf Harofeh Medical Center (affiliated to Sackler School of Medicine, Tel Aviv University), Zerifin 70300, Israel
R. LANGER
R. RON-EL
M. NEWMAN
A. HERMAN
E. CASPI

Correspondence: R. Langer

used for comparing skewed variables: the Mann–Whitney test for comparisons between groups and the Wilcoxon signed rank test for comparison within groups.

Results

Ninety-two patients had a colposuspension. Of these, 62 were diagnosed before the operation as having genuine stress incontinence (group A) and 30 as having combined genuine stress incontinence and detrusor instability. Table 1 summarizes the characteristics of these two groups of patients. The two groups were similar for mean age, parity and duration of symptoms before the operation. More patients in group A had had operations for urinary incontinence in the past but the difference was not statistically significant.

Clinically (Table 2) there was a significant reduction ($P<0{\cdot}001$) in symptoms of frequency, diurnal and nocturnal, urgency and urge incontinence ($P<0{\cdot}01$) between before and 3–6 months after operation in both groups. Two operative failures were encountered regarding stress incontinence, one in each group.

The cystometric and uroflowmetry results are presented in Table 3. There were no statistically significant differences between before and after operation for residual volume, maximal voiding pressure and peak flow rates in the two groups. In group A no differences were found in the pressure rise on filling or standing, while in group B there was a statistically significant reduction in pressure rise on filling ($P<0{\cdot}001$) and on standing ($P<0{\cdot}01$). A statistically significant decrease in the capacity was found after operation in both groups. In both groups the urethral pressure profiles showed no statistically significant changes regarding urethral length and closure pressure at rest. The pressure transmission ratio on coughing was greater than 100% in the proximal half of the urethra after operation in both groups. The two women in whom surgery failed had a postoperative pressure transmission ratio <100% throughout the entire length of the urethra. Combining the pre- and postoperative clinical and urodynamic results (Table 4) we found a significant reduction in symptoms regarding detrusor instability postoperatively. This reduction in symptoms occurred in both groups, from 24% pre-operatively to 10% post-

Table 1. Age, parity, duration of symptoms and previous operations for urinary incontinence in 92 patients

	Group A* (n = 62)		Group B† (n = 30)	
	Mean (SD)	Range	Mean (SD)	Range
Age (years)	44·3 (6·1)	33–73	49·8 (7·3)	29–70
Parity	3·2 (1·8)	1–8	3·2 (1·5)	0–8
Duration of symptoms (years)	4·9 (3·2)	1–15	4·8 (4·1)	1–17
Previous operations for urinary incontinence n (%)	12 (19%)		3 (10%)	

* Group A—patients with genuine stress incontinence.

† Group B—patients with combined genuine stress incontinence and detrusor instability.

Table 2. Clinical data before and after operation in the two groups

	Group A (n =62)		Group B (n = 30)	
	Before n (%)	After n (%)	Before n (%)	After n (%)
Frequency				
Diurnal	26 (42)	2 (3)*	19 (63)	4 (13)
Nocturnal	31 (50)	4 (6)*	20 (66)	6 (20)
Urgency	27 (43)	6 (10)*	24 (80)	10 (33)
Urge incontinence	15 (24)	6 (9)**	21 (70)	6 (20)
Stress incontinence	62 (100)	1 (2)*	30 (100)	1 (3)

Significance of difference between values before and after operation * $P<0{\cdot}001$, ** $P<0{\cdot}01$ (McNemar's paired χ^2).

Table 3. Urodynamic data before and after operation in the two groups

	Group A (n = 62)			Group B (n = 30)		
	Before	After	P	Before	After	P
Capacity (ml)	523·7 (450–600)	477·9 (430–550)	<0·02	505·7 (370–690)	475·8 (340–570)	<0·001
Residual (ml)	10·4 (0–100)	19·4 (0–100)	>0·05	13·4 (0–50)	15·7 (0–100)	>0·05
PR1* (cmH$_2$)	10·9 (8–14)	9·1 (5–16)	>0·05	18·2 (9–40)	5·4 (2–8)	<0·001
PR2† (cmH$_2$O)	4·7 (2–9)	4·8 (2–12)	>0·05	11·6 (6–28)	8·2 (0–20)	<0·01
Maximal voiding pressure (cmH$_2$O)	32·0 (20–45)	30·3 (15–50)	>0·05	41·0 (30–75)	38·5 (25–65)	<0·05
Peak flow rate (ml/s)	24·8 (15–45)	22·6 (15–40)	>0·05	22·6 (14–30)	21·0 (15–30)	>0·05

* PR1, Pressure rise on filling; † PR2, pressure rise on standing.
Results are mean (range) values.

Table 4. Clinical and urodynamic data of detrusor instability before and after operation in the two groups

	Group A (n = 62)			Group B (n = 30)		
Detrusor instability	Before n (%)	After n (%)	P	Before n (%)	After n (%)	P
Clinical	15 (24)	6 (10)	<0·01	22 (73)	10 (33)	<0·05
Urodynamic	0	17 (27)	<0·001	30 (100)	12 (40)	<0·001

operatively in group A (P<0·01) and from 73% to 33% in group B (P<0·05).

Urodynamically in group B, 40% of the patients (12/30) had cystometric findings of detrusor instability after operation compared with 100% with such findings before operation (P<0·001). In group A 17 patients (27%) had cystometric detrusor instability after operation compared with none before operation (P<0·001).

Discussion

Detrusor instability is a known complication of some forms of suprapubic surgery for genuine stress incontinence (Jarvis 1981) including the colposuspension operation (Cardozo *et al.* 1979). Of the 62 patients who had a pre-operative diagnosis of genuine stress incontinence only (group A), 17 (27%) had cystometric signs of detrusor instability after operation. These findings did not correspond to the clinical symptomatology of detrusor instability, frequency, urge and urge incontinence which were significantly reduced from 24% before operation to 9% after operation in this group. The precise aetiology and natural history of the development of postoperative detrusor instability are still unknown. In men, detrusor instability may be secondary to outflow obstruction and is often reversed by its relief (Turner-Warwick *et al.* 1973).

Colposuspension is thought to produce continence by elevation of the bladder neck and, possibly, by compression of the upper urethra. One might hypothesize that in those who developed instability after surgery, excessive urethral compression led to outflow obstruction and consequent detrusor instability. However, this is not the case as we could not find any changes in peak flow rates or maximal voiding pressures. These results were obtained 3–6 months postoperatively. No changes in the clinical symptomatology were observed at 1 year follow-up. We did not perform a repeat urodynamic investigation at that time but Steel *et al.* (1985) noted that most patients for whom urodynamic data were available 4 to 5 years after colposuspension remained unstable.

Pre-operative detrusor instability is often considered a contraindication for surgery (Arnold *et al.* 1973; Frimold *et al.* 1974). Stanton *et al.* (1978) discussed the factors which were associated with failed surgery for urinary incontinence and suggested that pre-operative detrusor instability was a major factor. Our results, although based on a small series, suggest that patients with pre-operative detrusor instability combined with urinary stress incontinence (group B) benefit from surgery. Surgery failed in one woman with stress incontinence and this was reflected by a low transmission ratio throughout the entire urethral length.

The value of the surgical approach to incontinence associated with detrusor instability is shown by our finding that 29 of the 30 patients (98%) with this diagnosis were dry post-operatively. Furthermore, in 12 of the 22 patients who had clinical features of detrusor instability—frequency, urge and urge incontinence—before operation, the symptoms disappeared after surgery. About 60% of the patients in group B had normal cystometric findings after surgery, as shown by the significant reduction in pressure rise on filling ($P<0{\cdot}001$) and on standing ($P<0{\cdot}01$). Similar results were found by Meyhoff *et al.* (1983) who operated upon patients with pure detrusor instability and found that 30% had normal cystometric findings subsequently. We have no satisfactory explanation why patients with pre-operative detrusor instability have their detrusor instability relieved by colposuspension or why detrusor instability develops in others after surgery.

References

Arnold, E. P., Webster, S. R., Loose, H., Brown, A. D. G., Turner-Warwick, R. T., Whiteside, C. G. & Jequier, A. M. (1973) Urodynamics of female incontinence. Factors influencing the results of surgery. *Am J Obstet Gynecol* **117**, 805-813.

Burch, J. C. (1961) Urethrovaginal fixation to Cooper's ligament for correction of stress incontinence, cystocele and prolapse. *Am J Obstet Gynecol* **81**, 281-289.

Cardozo, L. D , Stanton, S. L. & Williams, J. E. (1979) Detrusor instability following surgery for genuine stress incontinence. *Br J Urol* **51**, 204-207.

Frimold, M. C., Gammelgaard, P. H., Hald, T. & Olsen, K. P. (1974) Urological investigation in women with recurrent incontinence following gynecological surgery. *Urol Int* **29**, 163-171.

International Continence Society (1981) Fourth report on the standardization of terminology of lower urinary tract function. *Br J Urol* **53**, 333-335.

Jarvis, G J. (1981) Detrusor muscle instability—a complication of surgery? *Am J Obstet Gynecol* **139**, 219.

Meyhoff, H. H., Walters, S., Gerstberg, T. C., Olesen, K. P., Nordling, S , Pedersen, P H & Hald, T. (1983) Incontinence surgery in female motor urge incontinence. *Acta Obstet Gynecol Scand* **62**, 365-368.

Morgan, J. E. (1973) The suprapubic approach to primary stress incontinence. *Am J Obstet Gynecol* **115**, 316-320.

Stanton, S. L., Williams, J. E. & Ritchie, D. (1976) The colposuspension operation for urinary incontinence. *Br J Obstet Gynaecol* **83**, 890-895.

Stanton, S. L., Cardozo, L., Williams, J. E., Ritchie, D. & Alan, V. (1978) Clinical and urodynamic features of failed incontinence surgery in the female. *Obstet Gynecol* **51**, 515-520

Stanton, S. L. & Cardozo, L. D. (1979) Results of the colposuspension operation for incontinence and prolapse. *Br J Obstet Gynaecol* **86**, 693-697.

Steel, S. A., Cox, C. & Stanton, S. L. (1985) Long-term follow-up of detrusor instability following the colposuspension operation *Br J Urol* **58**, 138-142.

Turner-Warwick, R. T., Whiteside, C. G., Worth, P. H. L., Milroy, E. J. G. & Bates, C. P. (1973) A urodynamic view of the clinical problems associated with bladder neck dysfunctions and its treatment by endoscopic incision and trans-trigonal posterior prostatectomy *Br J Urol* **45**, 44-59.

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Sexually transmitted diseases including genital papillomavirus infection in male sexual partners of women treated for cervical intraepithelial neoplasia III by conization

P. BISTOLETTI, P. LIDBRINK

Summary. History and clinical prevalence of sexually transmitted diseases (STD), including genital human papillomavirus (HPV) infection, were studied in 60 sexual partners of 60 women previously treated for cervical intraepithelial neoplasia (CIN) III by conization. Investigations included serological and bacteriological screening, histopathology and colposcopy. A history of STD was reported by 20 men (33%), and 34 (57%) had signs of STD including genital HPV infection, 2 (3%) had a chlamydial infection, one had molluscum contageosum, 7 (12%) had genital warts and 24 (40%) had abnormal acetowhite epithelium, indicating HPV infection. The HPV lesions were principally subclinical and located on the glans penis and the prepuce. Colposcopy and application of acetic acid are essential for detection. The gynaecologist and venereologist must recognize the sexually transmitted nature of CIN, and the causal link between CIN and HPV infection. Assessment and treatment of the male sexual partner of women treated for CIN might be an essential part in disease control with the aim of preventing cervical cancer.

Cancer of the uterine cervix has been found to be strongly linked to sexual behaviour, in particular to early onset of sexual activity and high promiscuity in both partners (Editorial 1986). Human papillomavirus (HPV) infection has been identified as the most important sexually transmitted disease (STD) involved in the aetiology of cervical neoplasia (Kreider *et al.* 1985). It has also been shown that women with cervical intraepithelial neoplasia (CIN) III have an increased risk of developing cervical or vaginal invasive neoplasia and the risk is considerable in women with recurrent CIN or vulval intraepithelial neoplasia (VIN) (McEndoe *et al.* 1984). We have examined the prevalence of STD in regular sexual partners of women previously treated for CIN. We were particularly interested in the prevalence of genital HPV infection in the male partners of women with recurrent CIN or VIN.

Patients and methods

This prospective cross-sectional survey was approved by the local ethics committee. During 1986, we recruited 60 consecutive men who were current regular sexual partners of women previously treated for CIN III by cold knife or laser

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Huddinge University Hospital, Karolinska Institutet, S-141 86 Huddinge, Stockholm, Sweden
Department of Obstetrics and Gynaecology
P. BISTOLETTI

Department of Dermatology and Venereology
P. LIDBRINK

Correspondence: P. Bistoletti

conization. The median follow-up time after conization was 3 years. A history of previous diagnosis or treatment for genital warts or other venereal infections was obtained, followed by visual inspection of the meatus, prepuce, penile shaft, scrotum and perianal region. These areas were treated with 5% acetic acid and after 5 min inspected with a colposcope. A direct punch biopsy was taken if lesions were visible with the naked eye or acetowhite lesions were visible. Blood samples for serology of syphilis and human immunodeficiency virus (HIV) infection were obtained from 56 men and samples for culture of *Neisseria gonorrhoea* and *Chlamydia trachomatis* were obtained from 59. The diagnosis of HPV infection was based on the clinical findings of condyloma acuminata or the presence of abnormal acetowhite epithelium in the genital region, or the presence of histopathological criteria, which are considered to be pathognomonic for HPV infection (Meisels *et al.* 1977; Kadish *et al.* 1986).

Results

A history of previous STD was reported by 20 men (33%), gonorrhoea by 11, *Chlamydia trachomatis* infection by two, genital herpes virus by one, a combination of these by two and genital warts by four.

Clinical examination showed that 34 men (57%) had a STD: *Chlamydia* infection (two), molluscum contageosum (one), genital warts visible to the naked eye (seven), abnormal acetowhite epithelial lesions (24). The genital warts and the acetowhite lesions were located mainly on the prepuce (21), the glans (five) and penile shaft (five). Biopsies were taken from 26 men; lesions from 13 were characterized histopathologically as non-specific inflammation and in 13 biopsies histopathological signs of HPV infection were observed. Among those were three with concomitant dysplasia and one with a pre-invasive penile carcinoma. The prevalence of STD in partners of women with recurrent dysplasia, and women without recurrent dysplasia after conization, is shown in Table 1. Table 2 provides a summary of other studies of sexual partners of women with CIN and HPV infection together with a control series.

Discussion

In agreement with previous studies we found a high prevalence of previous and current STD, predominantly genital HPV infection, in male consorts of women with CIN (Levine *et al.* 1984; Sand *et al.* 1986; Sedlacek *et al.* 1986; Schneider *et al.* 1987). Although the women in the present study had been treated for CIN III by conization, still half the men had a genital papillomavirus infection. Obviously treatment of the CIN lesion by cone biopsy does not eliminate the genital HPV infection (unpublished observations) and these women might remain infectious. We do not know at present how infectious these women or their male sexual partners are. Genital HPV infection in the male partners is often subclinical. Therefore diagnosis is often missed and should be based on colposcopic assessment with acetic acid and biopsies (Sand *et al.* 1986; Sedlacek *et al.* 1986) or identification of HPV DNA.

The prevalence of STD and history of STD was higher in the group of partners of women with recurrent dysplasia, but the numbers are too few to make a reliable statistical analysis. If these findings are confirmed, it seems reasonable to examine the male partners of all women who have recurrent CIN after treatment for CIN III.

Finally we have to recognize the sexually transmitted nature of CIN, and the strong causal link between CIN and cervical HPV infection (Kreider *et al.* 1985). Our results fit the concept of the 'high-risk male' and the increased risk for cervical cancer in female partners of men who

Table 1. History and presence of sexually transmitted disease (STD) in male consorts of 15 women with and 45 without recurrent cervical intraepithelial neoplasia (CIN) or vulval intraepithelial neoplasia (VIN) after treatment for CIN III by conization

	Recurrent CIN/VIN in female partner	
Findings in male consorts	Present (*n* = 15) *n* (%)	Absent (*n* = 45) *n* (%)
STD history	6 (40)	14 (31)
Genital warts and/or acetowhite epithelium	10 (67)	21 (47)
HPV infection (biopsies)	4 (29)	6 (13)
HPV infection with atypia	1 (7)	3 (7)

Table 2. Findings in studies of male sexual partners of women with CIN and/or genital HPV infection

		Percentage with signs of HPV infection	
Reference	*n*	Acetowhite lesions or genital warts	HPV-DNA
Present study	59	52	
Levine *et al.* (1984)	34	53	
Sand *et al.* (1986)	90	69	
Sedlacek *et al.* (1986)	51	100	
Schneider *et al.* (1987)	40	50	65
Grussendorf-Conen *et al.* (1986) (normal control series)	530		5·8

are very promiscuous sexually (Editorial 1986). Adequate assessment of the male sexual partner(s) of women treated for CIN seems to be an essential part in control of CIN and the prevention of cervical cancer.

References

Editorial (1986) *Bull WHO* **64**, 607-618.

Grussendorf-Conen, E. I., de Villiers, E. M. & Gissmann, L. (1986) Human papillomavirus genomes in penile smears of healthy men (Letter). *Lancet* **ii**, 1092.

Kadish, A., Burk, R., Kress, Y., Calderin, S. & Romney S. (1986) Human papillomaviruses of different types in precancerous lesions of the uterine cervix: histologic, immunocytochemical and ultrastructural studies. *Hum Pathol* **17**, 384-392.

Kreider, J , Howtt, M., Wolfe, S. A., Barlett, G , Zaino, R., Sedlacek, T. & Mortel, R. (1985) Morphological transformation *in vivo* of human uterine cervix with papillomavirus from condyloma acuminata. *Nature* **317**, 639-641.

Levine, R., Crum, C., Herman, E., Silver, D., Ferency, A. & Richart, R. (1984) Cervical papillomavirus infection and intraepithelial neoplasia: a study of male sexual partners. *Obstet Gynecol* **64**, 16-20.

McEndoe, W., McLean, M., Jones, R. & Mullins, P. (1984) The invasive potential of carcinoma *in situ* of the cervix. *Obstet Gynecol* **64**, 451-458.

Meisels, A., Fortin, R. & Roy, M. (1977) Condylomatous lesions of the cervix. II Cytologic, colposcopic and histopathologic study *Acta Cytologica* **21**, 379-390.

Sand, P., Bowen, L., Blischke, S. & Ostergard, D. (1986) Evaluation of male consorts of women with genital human papillomavirus infection. *Obstet Gynecol* **68**, 679-681.

Schneider, A , Sawada, E., Gissmann, L & Shah, K. (1987) Human papillomaviruses in women with a history of abnormal Papanicolaou smears and in their male partners. *Obstet Gynecol* **69**, 554-562.

Sedlacek, T., Cunnane, M. & Carpiniello, V. (1986) Colposcopy in the diagnosis of penile condyloma. *Am J Obstet Gynecol* **154**, 494-496.

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The serum pregnancy-specific β_1-glycoprotein to beta-human chorionic gonadotrophin ratio as an index of prognosis in patients with choriocarcinoma

NORIAKI SAKURAGI, HITOSHI OHKUBO, RITSU YAMAMOTO, YOSHIHIRO SHIINA, TOSHINOBU TANAKA, KIHYOE ICHINOE, SEIICHIRO FUJIMOTO

Summary. The ratio of serum pregnancy-specific β_1-glycoprotein (SP1) to the β-subunit of human chorionic gonadotrophin (β-hCG) before and after chemotherapy was measured in 12 patients with metastatic choriocarcinoma. The ratios before chemotherapy ranged between 0·03 and 0·75, with a mean value of 0·34 (SD 0·21). The ratio increased to over 1·0 (1·05–53·3) after one or two courses of chemotherapy in seven of the 12 patients. These women achieved complete remission. In the other five patients who died of the disease due to drug resistance of the tumour, the ratio after chemotherapy was low (0·04–0·74) and tended to decline. These data suggest that the serum SP1/β-hCG ratio can be used to predict the prognosis of patients with choriocarcinoma.

Since the concept of primary chemotherapy for patients with trophoblastic diseases was accepted, many patients have been treated with chemotherapy alone, even if a histological diagnosis has not been confirmed (Li *et al.* 1956; Hertz *et al.* 1961). Because some patients are refractory to chemotherapy, the prognosis for invasive mole and choriocarcinoma has been assessed by several scoring systems (Ishizuka 1969; Hammond *et al.* 1973; Bagshawe 1976).

Recent advances in the purification and quantitation of trophoblastic proteins have created the possibilities for differentiation in the diagnosis and prognosis of trophoblastic neoplasia. In this report, we discuss the significance of the ratio of serum pregnancy-specific β_1-glycoprotein (SP1) to β-subunit of human chorionic gonadotrophin (β-hCG) in assessing the response to chemotherapy, and prognosis of the patients with choriocarcinoma.

Patients and methods

The study included 15 women with obvious metastatic trophoblastic diseases treated at the Gynaecology Department, Hokkaido University Hospital, Sapporo, Japan (Table 1). Changes in the ratio after tumour resection in patients without metastases cannot be regarded as a reflection of responsiveness of the tumour to chemotherapy but merely the reflection of the difference in the clearance rate of SP1 and β-hCG from the blood. Serum samples were obtained before the start of treatment, and weekly during chemotherapy. The final diagnosis (i.e. whether the patients had choriocarcinoma or invasive mole) was confirmed on the basis of histopathological findings of surgically resected specimens according to the criteria of

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Department of Obstetrics and Gynecology, Hokkaido University School of Medicine, Sapporo, Japan
NORIAKI SAKURAGI
HITOSHI OHKUBO
RITSU YAMAMOTO
YOSHIHIRO SHIINA
TOSHINOBU TANAKA
KIHYOE ICHINOE
SEIICHIRO FUJIMOTO

Correspondence: N. Sakuragi

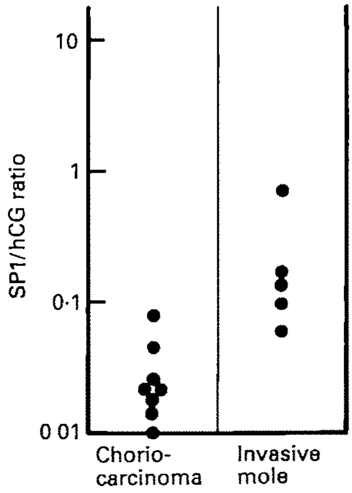

Fig. 1. Serum SP1/hCG ratio in patients with choriocarcinoma and invasive mole before treatment.

Novak & Seah (1954). Of the 15 patients 12 had choriocarcinoma and the remaining three had invasive mole. Combination chemotherapy with methotrexate and actinomycin-D was used in these women. Some patients with liver or brain metastases were treated additionally with radiation and a triple-agent regimen (methotrexate, actinomycin-D and cyclophosphamide). The dose of methotrexate was 0·3 mg/kg per day for 5 days. Actinomycin-D was used in dosage of 0·1 mg/10 kg per day for 5 days and cyclophosphamide at 2 mg/kg per day for 5 days. Each regimen was repeated with a 2-week interval as long as there was no severe liver dysfunction or bone marrow suppression.

The 12 patients with metastatic choriocarcinoma could be divided into two groups; those who died of the disease (five patients) and those who achieved complete remission (seven patients).

Serum SP1 was measured by radioimmunoassay with reagents produced by Behringwerke AG, West Germany. Serum hCG and β-hCG levels were radioimmunoassayed with reagents produced by CIS, France, as described previously (Sakuragi 1982). The interassay coefficient of variation (inter-CV) was 6·6% and intra-assay coefficient of variation (intra-CV) was 5·7% in this SP1 assay. Normal male serum samples with 10, 100, 1000 or 10 000 ng/ml of standard hCG(CR-119) added were assayed with this system and showed no cross-reaction with hCG. We could therefore ignore the interference of large amounts of hCG contained in the sera of patients with trophoblastic diseases. The sensitivity of this assay was 2–3 ng/ml.

The cross-reactivity in the homologous hCG assay system used here with standard β-hCG(CR-119-2) was 1·5%. The inter-CV and intra-CV were 5·5% and 6·9%, respectively.

The homologous β-hCG assay system used in this study cross-reacted with standard native hCG(CR-119) and α-hCG(CR-115) with rate of 6·7% and 0·4%, respectively. Values presented for β-hCG levels, therefore, are approximately the sum total of free β-hCG and cross-reacted native hCG. The inter-CV and intra-CV were 6·5% and 4·9%, respectively. The assay sensitivity was 0·2 ng/ml. SP1, hCG and β-hCG are produced and secreted by the syncytiotrophoblast (Tatarinov *et al.* 1976; Horne *et al.* 1976; Kasai & Yoshida 1979; Kasai *et al.* 1979). Concentrations of these substances are given in units of ng/ml in this study. Therefore the SP1/hCG and SP1/β-hCG ratio is not affected by the size of the trophoblastic cell mass and the value has no unit.

Student's *t*-test and the paired *t*-test were used to determine statistically significant differences.

Results

We found a significant difference in serum SP1/hCG and SP1/β-hCG ratio between patients with choriocarcinoma and those with invasive mole. In particular the SP1/β-hCG ratio of 1 clearly differentiated between the two groups as

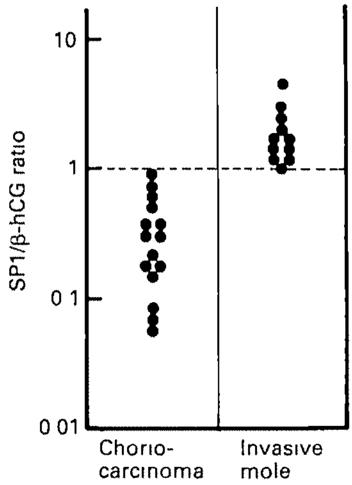

Fig. 2. Serum SP1/β-hCG ratio in patients with choriocarcinoma and invasive mole before treatment

noted previously (Sakuragi 1982, 1986) (Figs 1 & 2).

The change in the SP1/β-hCG ratio in patients with choriocarcinoma after admission is shown in Figs 3 and 4. In patients who died of the disease, the ratio tended to remain at a low level, while in those who achieved complete remission, the ratio tended to increase. To assess these findings more clearly, we compared the changes in the SP1/β-hCG ratios about a week after chemotherapy between the two groups. If the ratio was determined more than once between the chemotherapy courses, the highest value was used for analysis. In those who died of the disease, the ratio was low and tended to decline (Table 1). The mean SP1/β-hCG ratio before chemotherapy was 0·40. The mean ratio after the first and the second course of chemotherapy was 0·33 and 0·26, respectively (significantly less than before treatment, $P<0·01$ by the paired *t*-test).

In the remission group, the ratio increased in all patients after chemotherapy (Table 1). The mean SP1/β-hCG ratio before chemotherapy was 0·30, which was not significantly different from the ratio before treatment in the patients who subsequently died. The ratio rose to 4·47 after the first course of chemotherapy ($P<0·05$, by the paired *t*-test). The ratio increased further in several of the patients after the second course of chemotherapy. In two of seven patients, marker protein levels decreased to a non-detectable level after the second course of chemotherapy.

The ratios in patients with metastatic invasive mole increased after chemotherapy (Table 1). Before treatment, the mean ratio was 1·22, which was higher than in patients with choriocarcinoma ($P<0·01$, by Student's *t*-test). The ratio rose to 3·99 after the first, and to 13·7 after the second course of chemotherapy. Chemotherapy in this group was effective, and all achieved complete remission.

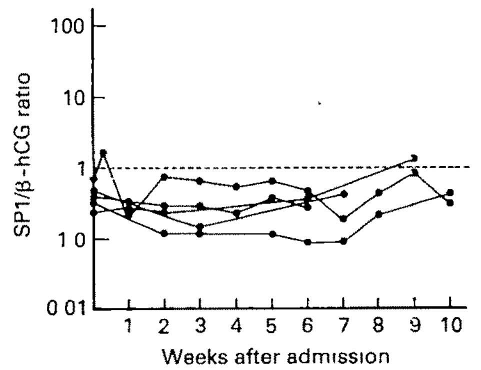

Fig. 3. Changes in serum SP1/β-hCG ratios after admission in patients with metastatic choriocarcinoma who subsequently died.

Patients whose serum SP1 concentration fell below sensitivity level in the first two courses of chemotherapy, either with metastatic choriocarcinoma or metastatic invasive mole, responded well to the therapy and achieved complete remission. Our results showed that increase in the SP1/β-hCG ratio after one or two courses of chemotherapy was associated with a good prognosis.

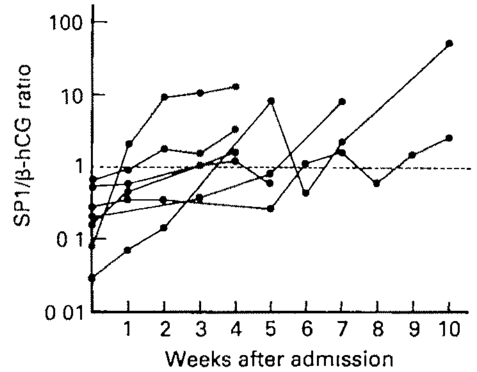

Fig. 4. Changes in serum SP1/β-hCG ratios after admission in patients with metastatic choriocarcinoma who achieved complete remission.

Discussion

Hertz *et al.* (1961) reported that methotrexate was equally effective in the treatment of choriocarcinoma and invasive mole. Later Ross *et al.* (1965) also found that histopathological diagnosis, antecedent pregnancy and prior operation exerted no influence on response to chemotherapy. Since those reports many patients with trophoblastic diseases have been treated with chemotherapeutic agents without surgery or without confirmation of the pathological diagnosis. However, in contrast to Hertz *et al.* (1961) there is evidence that histologically confirmed choriocarcinoma has a poorer prognosis than invasive mole (Bagshawe 1976; Katoh *et al.* 1979).

Recent work on trophoblastic proteins has created the possibilities for differentiation in the diagnosis and prognosis of trophoblastic disease. Molecular heterogeneity of hCG secreted by choriocarcinoma in sialic acid component or iso-

Table 1. Serum levels of pregnancy-specific β_1-glycoprotein (SP1) and beta human chorionic gonadotrophin (β-hCG) in 15 patients with metastatic trophoblastic disease before and after chemotherapy

				After chemotherapy					
	Before treatment			After first course			After second course		
Patient group	SP1 (ng/ml)	β-hCG (ng/ml)	SP1/ β-hCG	SP1 (ng/ml)	β-hCG (ng/ml)	SP1/ β-hCG	SP1 (ng/ml)	β-hCG (ng/ml)	SP1/ β-hCG
Choriocarcinoma									
Patients died									
1	280	770	0·36	11·0	78	0·14	10·0	29	0·34
2	1050	1530	0·68	62	84	0·74	90	158	0·57
3	42	108	0·38	11·5	35	0·34	5·5	19·5	0·28
4	1000	2850	0·35	1817	13 000	0·14	12·5	140	0·09
5	3050	12 400	0·25	424	1440	0·29	3·0	79	0·04
Mean	1084	3532	0·40	465	2927	0·33	24	85	0·26
Patients with remission									
6	4·0	148	0·03	44	5·0	8·80	80	1·5	53·3
7	55	320	0·17	10·0	21	0·47	5·3	3·8	1·39
8	6·9	33	0·21	7·7	0·9	8·75	—*	0·3	
9	109	145	0·75	60	28·5	2·10	—	1·6	
10	2·9	35	0·08	2·7	0·3	9·00	2·6	0·2	13·0
11	2050	3700	0·55	51	49	1·05	5·0	7·2	0·69
12	44	142	0·31	108	98	1·10	10·5	5·6	1·88
Mean	325	646	0·30	41	29	4·47	21	2·9	14·1
Invasive mole									
13	198	180	1·10	132	66	2·00	7·0	1·3	5·33
14	34	24·6	1·38	—	7·9		—	1·9	
15	2100	1780	1·18	2508	420	5·97	5950	270	22·0
Mean	777	662	1·22	880	165	3·99	1986	91	13·7

* Below assay sensitivity (<2 ng/ml)

electric point has been reported by some authors (Mizuochi *et al.* 1983; Yazaki *et al.* 1980). We reported previously that the serum SP1/β-hCG ratio is a useful marker for differentiating between choriocarcinoma and invasive mole. The ratio also seems to correlate with the degree of differentiation of trophoblastic cells (Sakuragi 1982, 1986). It is known that methotrexate, which is a DNA synthesis inhibitor, may induce differentiation of trophoblastic cells and alter their protein synthesis (Speeg *et al.* 1976; Friedman & Skehan 1979; Kuramoto *et al.* 1982). Thus, it might be expected that the serum SP1/β-hCG ratio in patients with choriocarcinoma sensitive to chemotherapeutic agents may increase after chemotherapy. In fact, the ratio did rise after chemotherapy in some of the patients with metastatic choriocarcinoma or metastatic invasive mole and they were sensitive to the drugs and achieved complete remission. On the other hand, the ratio remained low in those patients who died of the disease and were refractory to the chemotherapy. Although the number of cases studied so far is small, our results suggest that increases in the SP1/β-hCG ratio in patients with choriocarcinoma after chemotherapy indicate tumour sensitivity to the drug and a favourable prognosis. Thus the SP1/β-hCG ratio may be an important indicator for prognosis of patients with choriocarcinoma, as well as a means of differentiating between choriocarcinoma and invasive mole, as described previously (Sakuragi 1982, 1986).

Acknowledgments

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References

Bagshawe, K. D. (1976) Risk and prognostic factors in trophoblastic neoplasia. *Cancer* **38,** 1375-1385.

Friedman, S. J. & Skehan, P. (1979) Morphological differentiation of human choriocarcinoma cells induced by methotrexate. *Cancer Res* **39,** 1960-1967.

Hammond, C. B., Brochert, L. G., Tyrey, L., Creasman, W. T. & Parker, R. T. (1973) Treatment of metastatic trophoblastic disease: good and poor prognosis. *Am J Obstet Gynecol* **115,** 451-457.

Hertz, R., Lewis, J. & Lipsett, M. B. (1961) Five years' experience with the chemotherapy of metastatic choriocarcinoma and related trophoblastic tumors in women. *Am J Obstet Gynecol* **82,** 631-640.

Horne, C. H. W., Towler, C. M., Pugh-Humphreys, R G. P., Thomson, A. W. & Bohn, H. (1976) Pregnancy specific β_1-glycoprotein—a product of the syncytiotrophoblast. *Experientia (Basel)* **32,** 1197-1199.

Ishizuka, N. (1969) Diagnosis and therapy of destructive hydatidiform mole and chorionepithelioma. *J Jap Obstet Gynecol Soc* **21,** 1443-1448.

Kasai, K. & Yoshida, Y. (1979) Morphological study on the production and secretion mechanism of human chorionic gonadotropin(hCG). *Acta Histochem Cytochem* **12,** 283-291.

Kasai, K., Suzuki, H., Aochi, H. & Yoshida, Y. (1979) Localization, distribution and secretion of human chorionic gonadotropin in normal human chorionic tissue. *Acta Histochem Cytochem* **12,** 213-218.

Katoh, T., Kudoh, J. & Takamizawa, H. (1979) Study on procedure of treatment of trophoblastic disease. *Acta Obstet Gynaecol Jpn* **31,** 1921-1927.

Kuramoto, H., Hamano, M., Suzuki, M., Arai, M & Watanabe, K. (1982) Study on so-called "cellular effect" of methotrexate on choriocarcinoma and its mode of manifestation. *Acta Obstet Gynaecol Jpn* **34,** 187-195.

Li, M. D., Hertz, R. & Spencer, D. B. (1956) Effects of methotrexate upon choriocarcinoma and chorioadenoma. *Proc Soc Exp Biol Med* **93,** 361-366.

Mizuochi, T., Nishimura, R., Derappe, C., Taniguchi, T., Hamamoto, T., Mochizuki, M. & Kobata, A. (1983) Structures of the asparagine-linked sugar chains of human chorionic gonadotropin produced in choriocarcinoma. *J Biol Chem* **258,** 14 126-14 129.

Novak, E. & Seah, C. S. (1954) Choriocarcinoma of the uterus—study of 74 cases from the Mathieu Memorial Choriocarcinoma Registry *Am J Obstet Gynecol* **67,** 933-961.

Ross, G. T., Goldstein, D. P., Hertz, R., Lipsett, M. B. & Odell, W. D. (1965) Sequential use of methotrexate and actinomycin-D in the treatment of metastatic choriocarcinoma and related trophoblastic diseases in women. *Am J Obstet Gynecol* **93,** 223-229.

Sakuragi, N. (1982) Serum SP$_1$ and hCG-β subunit (hCG-β) levels in choriocarcinoma, invasive mole and hydatidiform mole—clinical significance of SP$_1$/hCG-β ratio. *Gynecol Oncol* **13,** 393-398.

Sakuragi, N. (1986) Determination of serum trophoblastic proteins in diagnosis and management of trophoblastic diseases. In *Trophoblastic Diseases* (Kihyoe, I., ed.), Igaku-Shoin, Tokyo, pp. 73-82

Speeg, K. V. Jr, Azizkhan, J. C. & Stromberg, K. (1976) The stimulation by methotrexate of human chorionic gonadotropin and placental alkaline phosphatase in cultured choriocarcinoma cells. *Cancer Res* **36,** 4570-4576.

Tatarinov, Y. S., Falaleeva, D. M., Kalashnikov, V. V & Tolokov, B. O. (1976) Immunofluorescent localization of human pregnancy-specific β-globulin in placenta and choriocarcinoma. *Nature* **260,** 263.

Yazaki, K., Yazaki, C., Wakabayashi, K. & Igarashi, M. (1980) Isoelectric heterogeneity of human chorionic gonadotropin: presence of choriocarcinoma specific components. *Am J Obstet Gynecol* **138,** 189-194.

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Term delivery following mid-trimester ruptured cornual pregnancy with combined intrauterine pregnancy. Case report

RAFAEL RON-EL, RAMI LANGER, ARIE HERMAN,
ELIAHU CASPI, YAN BUKOVSKY

Case report

A 38-year-old woman was admitted in the 14th week of her third pregnancy because of right low abdominal pain. Fifteen years previously the patient had had a right salpingo-oophorectomy for a ruptured right tubal pregnancy and this was followed by 9 years of secondary infertility. At laparoscopy she was found to have left peri-adnexal adhesions and these were removed surgically. Subsequently she conceived and gave birth to a healthy child in 1981. On admission the patient was in good physical condition. The physical examination was normal, the fetal heart was detected by Doppler ultrasound and the haemoglobin concentration was 9·9 g/dl.

On the second day after admission, the pain worsened. Peritoneal irritation appeared on the right side and the haemoglobin concentration dropped to 7·4 g/dl. An ultrasound scan showed two gestational sacs; one in the middle uterine cavity with a live fetus and the second, close to the right cornu, with a dead fetus.

A prompt explorative laparatomy revealed a haemoperitoneum of 1000 ml and a ruptured right uterine cornu. Products of pregnancy emerged from the site of the rupture and were removed carefully. The intrauterine sac was separated from the surgical site by a solid tissue. The corpus luteum was seen in the left ovary. The left tube was patent and several thin peritubal adhesions were noticed. The cornual margins were sutured in three layers and covered with the round ligament. The postoperative course was unremarkable and the patient was discharged on the seventh postoperative day and placed under observation in the outpatient high-risk clinic.

Elective caesarean hysterectomy was performed at 37 completed weeks gestation. A healthy female infant was born with an Apgar score of 10 at 1 min and a birthweight of 3·5 kg. There was no bulging or any different tissue thickness or colour of the myometrium in the right cornual site. At the patient's request hysterectomy for sterilization was performed. Both mother and child were sent home on the sixth postoperative day.

Discussion

Multiplication of the current rate of ectopic pregnancy (0·8%) with the rate of dizygotic twins (0·8%) gives a present theoretical rate of combined intrauterine and ectopic pregnancies of 1 in 15 000 (Richards *et al.* 1982). Nevertheless, experience has shown even higher rates of 1:7963 (Reece *et al.* 1983) and 1:6778 (Hann *et al.* 1984).

Since interstitial pregnancy is a rare event, the combination with intrauterine pregnancy is even rarer and has been described in only a few cases (Bisca & Felder 1960; Beckmann *et al.* 1984). Bisca & Felder (1960) described a patient who conceived 3 years after adnexectomy and cornual resection for a tubo-ovarian abscess and was operated on with a pre-operative diagnosis of an impending rupture through the site of the previous resected tube. An interstitial pregnancy was found and excised and the coexistent

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Department of Obstetrics and Gynecology, Assaf Harofeh Medical Center, Zerifin and Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel
RAFAEL RON-EL
RAMI LANGER
ARIE HERMAN
ELIAHU CASPI
YAN BUKOVSKY

Correspondence: R Ron-El

intrauterine pregnancy was left intact. The second patient reported by Beckmann *et al.* (1984) was operated on because of abdominal pain and an interstitial gestation in the early stage of the rupture was found. The existence of an intrauterine gestation was confirmed later.

Previous cornual resection as an aetiological cause of a uterine rupture, diagnosed post-partum, has been reported (Ferguson & Reid 1958). In our patient, the cornual rupture occurred at 13 weeks gestation, which is quite early. Excluding the possibility of spontaneous rupture of a scarred uterus in twin pregnancy, the hazard of recurrent ipselateral interstitial pregnancy following salpingectomy is well established (Weckstein 1985). Flusher (1959) mentioned that a simple cornual resection did not prevent this complication, since even a small portion of the tubal epithelium left in the uterine wall can act as a nidus for further recanalization.

In the patient reported by Bisca & Felder (1960), the intrauterine fetus was spontaneously aborted at 13 weeks gestation 5 days after the operation. We know of only one other case report (Beckmann *et al.* 1984) where the intrauterine pregnancy continued to term after resection of the coexistent interstitial pregnancy. Their case differs from ours in that the gestational age was only 6·5 weeks and they performed cornual resection to a depth of about one half of the myometrial thickness.

Lack of diagnostic features reduces clinical suspicion, and in many cases definite treatment has been delayed (Hayes & Haley 1984; Hann *et al.* 1984; Richards *et al.* 1982). Correct pre-operative ultrasound assessment of the intrauterine pregnancy is essential. We think that precise pre-operative diagnosis is not crucial, as long as laparotomy is not postponed. Being aware of the possibility of combined pregnancies enables us to establish correct pre-operative diagnosis avoiding delay in the preparation of the surgical team for the proper procedure.

References

Beckmann, C. R. B., Tomasi, A M. & Thomason, J. L. (1984) Combined interstitial and intrauterine pregnancy: Cornual resection in early pregnancy and cesarean delivery at term *Am J Obstet Gynecol* **149,** 83-85.

Bisca, B. V. & Felder, M. E. (1960) Co-existent interstitial and intrauterine pregnancy following homolateral salpingo-oophorectomy. Report of a case *Am J Obstet Gynecol* **79,** 263-265

Ferguson, R. K. & Reid, D. E (1958) Rupture of the uterus: A twenty-year report from the Boston Lying-in hospital *Am J Obstet Gynecol* **76,** 172-180.

Flusher, R. W. (1959) Tubal pregnancy following homolateral salpingectomy. *Am J Obstet Gynecol* **78,** 355-367.

Hann, L. E., Bachman, D. M. & McArdle, C. R. (1984) Co-existent intrauterine and ectopic pregnancy: A re-evaluation. *Radiology* **152,** 51-54.

Hayes, H R. & Haley, E. C. (1984) Intrauterine and ruptured tubal ectopic pregnancy: A diagnostic challenge. *Ann Emerg Med* **13,** 355-367.

Reece, E. A., Petrie, R. H., Sirmans, M. F., Finster, M. & Todd, W. D. (1983) Combined intrauterine gestations: A review. *Am J Obstet Gynecol* **146,** 323-330.

Richards, S. R., Stempel, L E. & Carlton, B. D. (1982) Heterotopic pregnancy: Re-appraisal of incidence. *Am J Obstet Gynecol* **142,** 928-930

Weckstein, L. N. (1985) Current perspectives on ectopic pregnancy. *Obstet Gynecol Surv* **40,** 259-272.

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Central pontine myelinolysis as a result of treatment of hyperemesis gravidarum. Case report

DAVID FRASER

Case report

An 18-year-old single West Indian girl was admitted with severe vomiting and a 1-month history of lethargy and malaise at 19 weeks gestation in her third pregnancy. This had not occurred in either of the previous pregnancies; all pregnancies were by the same partner.

On booking at 13 weeks gestation, she had appeared to be well and routine investigations were normal. Her weight was 102 kg. Apart from asthma, for which salbutamol aerosol (Ventolin, Allen & Hanburys) had been prescribed, there was no other relevant history. She failed to attend for her next three antenatal appointments and an ultrasound scan had not been performed.

On examination, she was dehydrated, anaemic and drowsy. Her weight was 85 kg, blood pressure was 110/60 mmHg and the pulse rate was 110 beats/min; a harsh systolic flow murmur was heard down the left sternal edge; the lung fields were clear. The symphysis–fundal height was 18 cm, and she was tender in both renal angles and suprapubically. Apart from drowsiness, there were no abnormal neurological findings. The plasma sodium concentration was 126 mmol/l, plasma potassium 2·3 mmol/l, blood urea 8·65 mmol/l and creatinine 210 mmol/l. The haemoglobin concentration was 8·8 g/dl and the arterial blood pH was 7·51. There was heavy ketonuria.

An ultrasound examination revealed oligohydramnios and a single viable fetus. The biparietal diameter was appropriate for the gestational age. Metabolic alkalosis and pre-renal uraemia secondary to hyperemesis gravidarum were diagnosed and intravenous rehydration was commenced.

During the next 48 h she received 16 litres of intravenous fluid (10 litres of normal saline, and 6 litres of 5% dextrose water with potassium supplements) and four units of packed red blood cells. The level of consciousness improved during the transfusion and the renal function returned to normal during the following days. The vomiting ceased. After the transfusion, the plasma sodium concentration was 145 mmol/l, potassium 4·0 mmol/l and blood urea 14·7 mmol/l.

A repeat ultrasound scan showed a normal amniotic fluid volume with an active fetus. Five days after admission her condition began to deteriorate. She exhibited an odd affect and failed to respond to verbal commands or communicate verbally. Bilateral sixth nerve palsies with horizontal nystagmus on attempted gaze in both directions were present with bilateral lower facial weakness. Although she moved all limbs normally, the tone in the upper limbs was increased; the upper limb deep tendon reflexes were normal. The knee jerks were absent and the ankle reflexes were depressed; both plantar responses were extensor. She was treated with 250 mg of thiamine intravenously (Parentrovite, Bencard) and her affect, ocular palsies and mental state improved; however, during the next 5 days signs of a spastic quadriparesis with a spastic dysarthria developed. Sensory examination was normal. Four weeks after admission the abnormal neurological signs began to improve, although a profound impairment of short-term memory was evident. An ultrasound scan at 23 weeks gestation confirmed a normal amniotic fluid volume and a well-grown and structurally normal fetus.

Spontaneous labour occurred at 32 weeks gestation and a live female infant weighing 1·98 kg was born vaginally. The baby was monitored

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Academic Department of Obstetrics and Gynaecology, King's College School of Medicine and Dentistry, Denmark Hill, London SE5 8RX
DAVID FRASER *Research Fellow/Honorary Registrar*

appropriately but required no special support and was discharged 3 weeks later.

Six months after discharge the patient exhibited a deficit of short-term memory, spastic dysarthria and trunkal ataxia, but 12 months after the illness only the memory disturbance persisted.

The infant has remained well and is developing normally.

Discussion

Nausea and vomiting occur commonly during the first trimester, complicating up to 50% of normal, singleton pregnancies (Klebanoff *et al.* 1985). In most women these features are minor and self limiting but in a small proportion the vomiting persists. If it is prolonged and intractable the descriptive term of hyperemesis gravidarum or 'pernicious vomiting of pregnancy' is applied; this occurs in approximately 2–3 women per 1000 total births (Fairweather 1968). The metabolic consequences include depletion of electrolytes (especially hydrogen, potassium, sodium and chloride ions), leading eventually to a deficiency of essential vitamins and co-factors such as thiamine (vitamin B1), pyridoxine (vitamin B6), cyanocobalamin (vitamin B12), and folate. Malnutrition due to hyperemesis gravidarum can be accompanied by neurological complications, notably a peripheral neuropathy due to deficiency of pyridoxine and cyanocobalamin, and, rarely, Wernicke's encephalopathy due to thiamine deficiency (Reuler *et al.* 1985; Lavin *et al.* 1983).

My patient is the first report of a young woman who developed central pontine myelinolysis and Wernicke's encephalopathy following the rapid correction of dehydration and electrolyte imbalance due to severe hyperemesis gravidarum. She survived and subsequently was delivered of a normal infant.

My patient exhibited signs of a peripheral neuropathy and Wernicke's encephalopathy. She also developed signs suggesting the clinical diagnosis of central pontine myelinolysis with a spastic quadriparesis which occurred shortly after the rapid correction of fluid and electrolyte imbalance. My patient is atypical in that the initial serum sodium (126 mmol/l) was rather higher than might have been predicted from previous reports of the neurological sequelae following correction of hyponatraemia, where the serum sodium is usually lower than this, typically below 115 mmol/l (Sterns *et al.* 1986).

Central pontine myelinolysis is a symmetrical focus of myelin destruction at the centre of the basal pons. The aetiology is poorly understood but experimental studies implicate the rapid and excessive correction of electrolyte disorders, especially hyponatraemia, as being important (Messert *et al.* 1979; Norenberg *et al.* 1982; Laureno 1983; Norenberg & Papendick 1984). Nearly all other cases of so-called 'osmotic demyelination syndrome' have occurred as an avoidable complication of overenthusiastic fluid therapy and the condition is particularly common in malnourished alcoholics (Narins 1986). The majority of such patients are severely ill and the diagnosis is made *post mortem.* However, neither alcoholism nor overcorrection of hyponatraemia is a prerequisite for this complication, and in this patient it arose as a result of the rapid treatment of a complication of pregnancy and also following dehydration. Thus, electrolyte replacement in women with hyperemesis is not without risk and this case illustrates two particularly important points.

First, the need for cautious rehydration in cases of hyperemesis gravidarum. The duration of hyponatraemia is apparently a risk factor and the development of central pontine myelinolysis has been linked to the speed of correction of chronic hyponatraemia, demyelination usually occurring where the sodium is corrected by more than 12 mmol/l per day. In this case the serum sodium rose by 19 mmol/l in the first 48 h of treatment. The risk of demyelination can be minimized by avoiding rapid or excessive correction of a chronic electrolyte disturbance (Laureno 1983; Norenberg & Papendick 1984; Sterns *et al.* 1986).

Second, the importance of adequate thiamine repletion in malnourished patients treated with glucose-containing intravenous fluids. In this case the diagnosis of Wernicke's encephalopathy was not immediately obvious and this, unfortunately, resulted in a delay in thiamine administration. Although this patient made a remarkable recovery from the central pontine myelinolysis, it is likely that her major residual disability—persisting memory deficit—is due to the Wernicke's encephalopathy.

Acknowledgments

I wish to thank Mr M. I. Whitehead and Dr J. Moxham for their permission to report this case.

I am also indebted to Dr P. D. Thompson, Senior Registrar in Neurology, for his invaluable help in the preparation of the manuscript.

References

Fairweather, D. V. I. (1968) Nausea and vomiting in pregnancy. *Am J Obstet Gynecol* **102**, 135-175.

Klenbanoff, M A., Koslowe, P. A., Kaslow, R. & Rhoads, G. G (1985) Epidemiology of vomiting in early pregnancy. *Obstet Gynecol* **66**, 612-616.

Laureno, R. (1983) Central pontine myelinolysis following rapid correction of hyponatraemia *Ann Neurol* **13**, 232-242.

Lavin, P. J. M., Smith, D., Kori, S. H. & Ellenberger, C. (1983) Wernicke's encephalopathy: A predictable complication of hyperemesis gravidarum. *Obstet Gynecol* **62**, 135-155.

Messert, B., Orrison, W. W., Hawkins, M. J. & Quaglieri, C E. (1979) Central pontine myelinolysis. Considerations on aetiology, diagnosis and treatment. *Neurology* **29**, 147-160

Narins, R. G. (1986) Therapy of hyponatraemia. *N Engl J Med* **314**, 1573-1574

Norenberg, M D., Leslie, K. O. & Robertson, A. S (1982) Association between rise in serum sodium and central pontine myelinolysis. *Ann Neurol* **11**, 128-135

Norenberg, M. D. & Papendick, R. E. (1984) Chronicity of hyponatraemia as a factor in experimental myelinolysis. *Ann Neurol* **15**, 544-547.

Reuler, J. M., Girard, D. E. & Cooney, T. G. (1985) Wernicke's encephalopathy. *N Engl J Med* **314**, 1035-1039.

Sterns, R. H., Riggs, J. E. & Schochet, S S Jr (1986) Osmotic demyelination syndrome following correction of hyponatraemia. *N Engl J Med* **314**, 1535-1542.

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Transient hyperthyroidism in a pregnancy with hydrops fetalis. Case report

T. T. LAO, R. K. H. CHIN, A. CHAN

Case report

A 27-year-old Chinese primigravida was admitted to hospital at 30 weeks gestation with a 4-day history of marked ankle oedema. Blood pressure was 130/90 mmHg and there was three-plus proteinuria and oedema. There was no relevant family or past medical history. Initial investigations showed a haemoglobin of 10·8 g/dl and a platelet count of 145×10^9/l, a blood urea of 4·1 mmol/l and creatinine of 87 μmol/l. The plasma urate was markedly elevated to 0·55 mmol/l. Culture of the midstream urine yielded no pathogens. Ultrasound scanning revealed a single live fetus with a biparietal diameter equal to the mean value of 27 weeks gestation. There was gross fetal ascites with marked oligohydramnios. The placenta measured 8 cm at its thickest part.

On the following day the patient was found to have tachycardia at rest and blood was then taken for estimation of thyroid function. On the third day, oliguria was noted and the blood urea and creatinine rose to 5·2 mmol/l and 108 μmol/l respectively. In view of these findings, labour was induced with a prostaglandin E_2 vaginal pessary (3 mg) followed by an intravenous oxytocin drip. A hydropic male fetus weighing 1520 g was born alive 6 h later but died shortly afterwards. The placenta weighed 600 g. Agarose electrophoresis of cord blood demonstrated the presence of haemoglobin Bart's (83%) and haemoglobin Portland. Although both parents had a microcytic and hypochromic blood picture, agarose electrophoresis showed no abnormal haemoglobin patterns. Because of an initial high thyroxine result, the maternal thyroid function was reassessed on days 3 and 6 postpartum when the pulse rate returned to below 100 per min. The results are shown in Table 1. On subsequent follow-up, there were no features of thyrotoxicosis.

Discussion

In Hong Kong, the commonest cause (81%) of non-immune hydrops fetalis is homozygous alpha-thalassaemia (Liang *et al.* 1985). Pre-eclampsia is a common complication in these pregnancies, the incidence being as high as 61% (Liang *et al.* 1985). The presentation of pre-eclampsia is usually in the early third trimester, and features of hydrops fetalis are usually obvious on ultrasound scanning when pre-eclampsia is diagnosed. Because homozygous alpha-thalassaemia is a lethal condition, it is our established practice to terminate the pregnancy as soon as possible to avoid complications of severe pre-eclampsia in the patient.

In our patient, the elevated thyroxine and triiodothyronine concentrations as well as free thyroxine index are strongly suggestive of hyperthyroidism, although the only clinical feature was a persistent resting tachycardia of above 100 beats/min. This state of hyperthyroidism was of recent onset, as the erythrocyte zinc concentration was not decreased (Lao *et al.* 1987). The subsequent spontaneous and rapid return of thyroid hormones to normal level indicated that this was a transient event, a condition similar to that described in molar pregnancy (Hershman & Higgins 1971) and normal pregnancy with hyperemesis gravidarum (Chin *et al.* 1987).

Beta-human chorionic gonadotrophin (β-hCG) was shown to possess in-vitro thyroid stimulating activity (Uchimura *et al.* 1976) and was believed to be the thyrotrophin in molar pregnancies (Hershman & Higgins 1971) and

Department of Obstetrics and Gynaecology, Prince of Wales Hospital, Shatin, Hong Kong
T. T. LAO *Lecturer*
R. K. H. CHIN *Senior Medical Officer*
A. CHAN *Medical Officer*

Correspondence: Dr T. T. Lao

Table 1. Thyroid function and human chorionic gonadotrophin before and after delivery

	30^{+2} weeks gestation	Postpartum Day 3	Postpartum Day 6	Normal range
Total thyroxine (nmol/l)	340	96	79	46–140
Total triiodothyronine (nmol/l)	3·7	0·4	—	1·0–3·1
Thyroid stimulating hormone (m-i.u /l)	4·4	1·7	1·8	0·4–5·2
T3 uptake (%)	37	28	—	24–38
Free thyroxine index	125·8	26·9	—	—
Beta-human chorionic gonadotrophin (i.u./ml)	1950	17	3·46	—
Erythrocyte zinc (μmol/l r.b.c.)	321·1	313·8	277·4	162·4–338·1

hyperemesis gravidarum (Lao *et al.* 1986; Chin *et al.* 1987). The change in thyroxine concentration in our patient was paralleled by the change in the circulating concentration of β-hCG, and at presentation the β-hCG concentration in our patient was very high (1 950 000 i.u./l). The high circulating level of hCG was probably related to the relatively large placental mass for the gestation, as the birthweight: placental weight ratio was 2·5:1. The association between a high β-hCG concentration and pre-eclampsia in this patient is interesting, because significantly higher serum β-hCG levels have been found in primigravid patients with proteinuric pre-eclampsia than in matched controls (Said *et al.* 1984).

The low T3 syndrome, reported before in pre-eclamptic patients (Osathanondh *et al.* 1976), was found in our patient 3 days after delivery when the triiodothyronine concentration dropped from 3·7 mmol/l to 0·4 mmol/l. This suggests that the low T3 syndrome is the result of clinical pre-eclampsia that had occurred for a certain length of time. An alternative explanation in our patient is that the fall in triiodothyronine represented the recovery stage of transient hyperthyroidism.

References

Chin, R. K. H., Lao, T. T. H., Cockram, C. S , Swaminathan, R. & Panesar, N. S. (1987) Transient hyperthyroidism in pregnancy. Case report. *Br J Obstet Gynaecol* **94,** 483–484.

Hershman, J. M O. & Higgins, H. P. (1971) Hydatidiform mole—A cause of clinical hyperthyroidism. Report of two cases with evidence that the molar tissue secreted a thyroid stimulator. *N Engl J Med* **284,** 573-577.

Lao, T. T. H., Chin, R. K H., Cockram, C S. & Panesar, N. S. (1986) Transient hyperthyroidism in hyperemesis gravidarum. *J R Soc Med* **79,** 613-615

Lao, T. T. H., Chin, R. K. H., Swaminathan, R., Panesar, N. S. & Cockram, C. S. (1987) Erythrocyte zinc in differential diagnosis of hyperthyroidism of pregnancy: A preliminary report *Br Med J* **294,** 1064-1065.

Liang, S. T., Wong, V. C. W., So, W. W. K., Ma, H. K., Chan, V. & Todd, D. (1985) Homozygous α-thalassaemia: clinical presentation, diagnosis and management. A review of 46 cases. *Br J Obstet Gynaecol* **92,** 680-684.

Osathanondh, R., Tulchinsky, D. & Chopra, I J (1976) Total and free thyroxine and triiodothyronine in normal and complicated pregnancy. *J Clin Endocrinol Metab* **42,** 98-104

Said, M. E , Campbell, D M., Azzam, M. E. & MacGillivray, I. (1984) Beta-human chorionic gonadotrophin levels before and after the development of pre-eclampsia. *Br J Obstet Gynaecol* **91,** 772-775.

Uchimura, H., Nagataki, S., Tabuchi, T , Mizuno, M. & Ho, K. (1976) The thyroid stimulating activity of highly purified preparations of human chorionic gonadotrophin. In *Thyroid Research* Proceedings of the Seventh International Thyroid Conference. Boston, Massachusetts, June 1975 (Robbins, J. & Braverman, L. E., eds), Excerpta Medica, Amsterdam/Oxford, pp 37-40.

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Amnionitis caused by *Propionibacterium acnes*. Case report

C. S. REED, R. G. FELDMAN, R. M. COCHRANE

Case report

A 34-year-old Ghanaian bank clerk was admitted to hospital as an 'in-utero' transfer. The duration of the pregnancy was assessed at 25 weeks. She had a history of dark red vaginal bleeding associated with regular uterine contractions for the previous 6 h.

This was her fourth pregnancy: the first, in 1976, resulted in delivery by emergency caesarean section at 38 weeks gestation for fetal distress; the second, in 1979, ended in a normal delivery at 40 weeks gestation; the third, in 1983, was terminated after 8 weeks.

The present pregnancy had been complicated by hyperemesis during the first trimester. At 20 weeks gestation, fetoscopy was performed to obtain cord blood for electrophoresis, since both parents had sickle cell trait; the fetal blood was normal. Ultrasound scan at 17 weeks confirmed the dates. After an episode of vaginal bleeding at 22 weeks gestation, another scan showed a low-lying posterior placenta, but no evidence of abruption or any other abnormality.

On examination the patient seemed relaxed with a pulse rate of 80/min, blood pressure 105/65 mmHg and temperature 36 °C. Her uterus was contracting every 5 min. The fundal height was 26 cm, and vaginal examination showed that the cervix was fully effaced, soft, and 2 cm dilated. An ultrasound scan performed on the labour ward demonstrated a single live fetus with a breech presentation and an estimated weight of 750 g. The placenta was clear of the cervical os and there was no evidence of an abruption.

The results of initial investigations were as follows: haemoglobin 12·9 g/dl, platelets 252 × 10^9/l, blood group O Rhesus positive. An intravenous infusion of ritodrine was established to suppress uterine contractions, and the fetus was continuously monitored cardiotocographically.

Amniocentesis, under ultrasound control to obtain a sample for culture, produced 10 ml of murky fluid which was found to contain numerous pus cells, moderate red blood cells, and numerous Gram-positive rods. Within an hour tocolysis was stopped, blood cultures were taken, and treatment with penicillin, gentamicin, and metronidazole was given.

Four hours after stopping the tocolytic therapy, a spontaneous breech delivery occurred and a live male infant was born weighing 774 g. Apgar scores were 7 at 1 min, and 9 at 5 min. He was electively intubated, transferred to the neonatal intensive care unit, and treated with penicillin and gentamicin from birth. He did well, breathing spontaneously after 3 days. He was fed with his mother's expressed breast milk from the second day of his life, and subsequently gained weight.

The mother had a normal puerperium and was discharged home 5 days postpartum.

Findings

Culture of the amniotic fluid grew *Propionibacterium acnes* which was also isolated from the anaerobic bottle of the maternal blood cultures. Placental cultures were sterile, as were the screening cultures from the infant, including a gastric aspirate.

The *P. acnes* was identified by Minitek (profile number 3500120) and gas-liquid chromatography (an acetic acid peak and a large propionic acid peak). It was fully sénsitive to penicillin, tetracycline, vancomycin, rifampicin, fucidic acid, clindamycin, azlocillin, imipenem, moxalactam, ciprofloxacin, ticarcillin, cefotaxime, teicoplanin, cefuroxime, cephalexin and

University College Hospital, London WC1E 6AU
Department of Clinical Microbiology
C. S. REED *Registrar*
R. G FELDMAN *Senior Registrar*

Department of Obstetrics and Gynaecology
R. M. COCHRANE *Registrar*

Correspondence: C. S. Reed, Senior Registrar, Department of Clinical Microbiology, St Stephen's Hospital, London SW10 9TH

ceftazidime. It was resistant to erythromycin, cefoxitin and metronidazole.

To assess the significance of this organism, a fluorescent antibody test was performed on paired maternal sera, and a single convalescent serum from the infant. The antigen used was an overnight suspension of the organism isolated from the amniotic fluid, which was then centrifuged, and the deposit resuspended in saline. Hendley–Essex 12-spot teflon-coated slides were prepared, with 5 µl of the suspension placed on each spot. These were dried in air at 37 °C, and then fixed in 10% methanol for 5 min. Doubling dilutions of the maternal and infant sera were made, up to a dilution of 1 in 128; 5–10 µl of each serum dilution were placed on spots on the prepared slides. The slides were incubated in a moist chamber at 37 °C for 30 min, washed in distilled water, rinsed three times in phosphate-buffered saline, then washed again in distilled water, and blot dried. Each spot was covered with freshly prepared fluorescein-labelled anti-human globulin and the slides reincubated at 37 °C for 30 min, followed by further washing as before. A coverslip was placed on the slide, which was then examined under oil immersion by fluorescent microscopy.

The acute maternal serum, taken on admission, had no detectable antibody; the convalescent maternal serum, taken 20 days after admission, had an antibody titre >1/128. The infant's convalescent serum, taken 14 days after birth, also had an antibody titre of >1/128.

Comment

P. acnes is a Gram-positive, non-sporeforming, facultatively anaerobic bacillus, often having a diphtheroidal cellular morphology. It is predominantly found in skin flora and was believed to be involved in the pathogenesis of acne. It is also part of the normal flora in the nasopharynx, mouth, intestine, and urogenital tract. It is an occasional contaminant of blood cultures and other body fluids collected by skin penetration. Rarely, it is a cause of endocarditis, of prosthetic joint infections, or of central nervous system shunt infections.

Although *P. acnes* has not been associated with amnionitis, it has been isolated from amniotic fluid in an uninfected patient previously (Maye *et al.* 1983). In the present patient the isolation of *P. acnes* from amniotic fluid and maternal blood cultures, as well as the positive serology in both mother and infant, confirm that this was an infection. The organism was not isolated from the infant, but the antibody may have arisen from a successfully treated infection.

The route of infection is not known. Contamination of the amniotic fluid during amniocentesis seems most unlikely, as the direct Gram-stain of the amniotic fluid showed numerous pus cells and Gram-positive bacilli. Infection via the genital tract is more plausible, either in a manner similar to that of Group B streptococci (Dasa & Trevenen 1984), or introduced at the time of fetoscopy. In a series of 796 fetoscopies, however, less than 0·5% were complicated by amnionitis, resulting in loss of the fetuses within 48 h of fetoscopy (Nicolaides & Rodeck 1985). In our patient fetoscopy was performed nearly 5 weeks before the onset of preterm labour.

Amniotic infection *per se* is known to be associated with the early onset of labour. In our patient, where the infecting organism was *P. acnes*, it is interesting to note that prostaglandin-like substances have been extracted from this organism (Berlin *et al.* 1980). These substances were shown to have a powerful vasoconstrictor activity on human umbilical vessels about equipotent to PGE_2, which is used to induce labour. We suggest that the early onset of labour in this patient might have been due not only to her amniotic infection, but also to the substances produced by the infecting organism.

Acknowledgments

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References

Berlin, E., Hellgren, L., Thulesius, O. & Vincent, J (1980) Prostaglandin-like substances in *Propionibacterium acnes* IV. Effect on isolated human vessels. *Experientia* **36**, 197-198.

Dasa, D. J. & Trevenen, C. L. (1984) Intrauterine infections with Group B beta-haemolytic streptococci. *Br J Obstet Gynaecol* **91**, 237-239.

Maye, D P., Filthuth, I., Pugin, P., Waldvogel, F. & Herrman, W. L. (1983) Bacteriological study of amniotic fluid during labor. *Acta Obstet Gynecol Scand* **62**, 603-607

Nicolaides, K. H. & Rodeck, C. H. (1985) Role of fetoscopy in perinatal medicine In *Recent Advances in Perinatal Medicine 2* (Chiswick, M L., ed), Churchill Livingstone, Edinburgh, pp 1-18

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Cervical stenosis after cone biopsy during post-pregnancy amenorrhoea. Case reports

D. MONCRIEFF, S. A. STEEL

Case reports

Patient no. 1

A 32-year-old Caucasian woman had moderate dyskaryosis on a cervical smear taken when she booked for antenatal care in her third pregnancy. Earlier that year three cervical smears had all shown dyskaryosis. Colposcopy, performed at 19 weeks gestation, suggested cervical intraepithelial neoplasia (CIN) 2/3. The colposcopy was repeated 3 months postnatally, and biopsies confirmed CIN 3 extending into the cervical canal. One month later (4 months postnatally) a cone biopsy of the cervix was performed by knife excision of a cone of cervical tissue including all non-iodine staining ectocervix and extending between 1 and 2 cm up the cervical canal. Dilatation of the cervix to Hegar 8 followed by curettage was performed to exclude disease in the endocervix or uterine cavity. Four polyglycolic acid (Dexon) sutures were inserted, two laterally, one anteriorly and one posteriorly, without inversion of the tissue edges, to secure haemostasis. The patency of the cervical canal was confirmed at the end of the operation by insertion of a uterine sound through the cervical canal. There were no early postoperative complications.

The histological report showed CIN 3 with clear resection margins. From the time of her cone biopsy until review 3 months later the patient continued to breast-feed and was amenorrhoeic. On speculum examination no external cervical os could be seen. She began on oral contraceptives and after completing one packet had no withdrawal bleed, and then presented with severe period-like pain. Dilatation and curettage was performed under general anaesthesia and a small amount of blood was released. Three months later the patient had still not menstruated and the cervix again appeared stenosed. Incision and dilatation of the cervix was repeated, old blood released, and a Foley catheter was left within the cervical canal for 2 days. One month later the patient complained of pain, and a pelvic ultrasound scan suggested a haematometra. The cervix was again dilated under general anaesthesia and a size 36 mm Robinson drain was inserted into the uterine cavity and sutured with polyglycolic acid Dexon to the cervix. The drain fell out 10 days later when the sutures dissolved. One month later she still complained of pain and on examination the external os was again completely stenosed. Total abdominal hysterectomy was advised and at laparotomy, free blood was found in the peritoneal cavity. She made an uneventful postoperative recovery. Histological examination of the cervix after hysterectomy revealed complete stenosis of the cervical canal.

Patient no. 2

A 28-year-old Caucasian woman first presented in 1983 when she had a normal cervical smear and cryocautery to the cervix was performed for a cervical 'erosion'. Two years later (5 months postnatally) she underwent colposcopy after a cervical smear taken at the postnatal clinic showed moderate dyskaryosis. Colposcopic biopsy revealed CIN 3 with mosaicism clinically extending into the cervical canal. Two months later a cervical cone biopsy was performed by a different surgeon but using the same techniques as described for patient 1. Postoperative compli-

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Department of Obstetrics and Gynaecology, St Helier Hospital, Carshalton, Surrey
D. MONCRIEFF

Department of Obstetrics and Gynaecology, St George's Hospital, Tooting, London SW17
S A STEEL

Correspondence. Dr D. Moncrieff, St Helier Hospital, Carshalton, Surrey

cations included a primary haemorrhage at 6 h which was controlled with a vaginal pack, and a secondary haemorrhage on day 15 which was also treated with a vaginal pack and antibiotics. The histological report confirmed CIN 3 with clear resection margins.

Three months postoperatively she had still not menstruated. Her partner had been using a sheath for contraception. No external os could be seen. One month later she was admitted as an emergency with severe abdominal pain. A pelvic ultrasound scan suggested a haematometra and the external os was incised under general anaesthesia releasing 50 ml of old blood. An inflated Foley's catheter balloon was left within the uterine cavity for 24 h. An oral contraceptive was prescribed, after which the patient experienced regular withdrawal bleeding.

Comments

Stenosis of the uterine cervix is a recognized complication following cone biopsy for CIN. Luesley *et al.* (1985) reported a stenosis rate of 17% with 1·3% presenting with haematometra. A literature search has not revealed any specific reference to post-conization stenosis as a particular risk in the postnatal patient who still has amenorrhoea. We report two such cases presenting as haematometra when cervical cone biopsy was performed while both women were still amenorrhoeic following childbirth.

Both had histologically confirmed CIN extending into the cervical canal on postnatal colposcopic assessment and were therefore unsuitable for local ablative therapy. The cone biopsies were performed 4 and 7 months respectively after normal vaginal delivery and before menstruation had recommenced. The method used for the surgical excision of the cervical cone is detailed in patient no. 1. It is the method routinely used by both authors and has not resulted in cervical stenosis in any other patient. In addition the patency of the internal cervical os and cervical canal had been checked at the end of both operations. The women each presented 4 months later with symptoms of menstruation and severe lower abdominal pain but no vaginal bleeding. An ultrasound scan showed haematometra in both patients.

We suggest that lack of menstruation may increase the risk of cervical stenosis which may prove difficult to treat. A regular menstrual flow should probably be re-established or initiated with hormone therapy after delivery and before cone biopsy. Alternatively, the insertion of an intrauterine contraceptive device at the time of operation could be considered.

Reference

Luesley, D M., McCrum, A , Terry, P. B. *et al.* (1985) Complications of cone biopsy related to the dimensions of the cone and the influence of prior colposcopic assessment. *Br J Obstet Gynaecol* **92,** 158-164.

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Premature menopause associated with autoimmune oophoritis. Case report

C. D. A. WOLFE, R. W. STIRLING

Case report

A 30-year-old Caucasian woman presented with a 3-year history of amenorrhoea and hot flushes. Menarche was at the age of 15 and her menstrual cycle had been regular previously. She had four full-term normal pregnancies and had undergone a laparoscopic clip sterilization 1 year before the onset of symptoms. Initial investigations showed serum gonadotrophin levels to be elevated (FSH 52 i.u./l, LH 136 i.u./l) with a normal prolactin level. At laparoscopy her ovaries appeared small and inactive. Thyroid function tests were normal. She was treated with Cyclo-Progynova but her symptoms persisted and treatment was changed to Prempak, 0·625 mg, after which she experienced menorrhagia. Endometrial curettings revealed proliferative endometrium. Prempak, 1·25 mg, was started but as she remained symptomatic, a total abdominal hysterectomy and bilateral oophorectomy was performed.

Histopathological sections of the uterus and cervix displayed a proliferative endometrium and low grade endocervicitis. Both ovaries measured 3 × 1·5 × 1 cm and sections of both ovaries showed a thickened fibrous capsule. Primordial follicles were numerous in both ovaries. The striking feature was of an inflammatory cell infiltrate in the walls of numerous developing follicles. This was composed of lymphocytes and plasma cells (Figs 1 & 2); a smaller number of inflammatory cells were seen in the ovarian stroma. Luminal haemorrhage and degenerative changes were associated with the inflammatory cell infiltrate. Corpora albicans were present indicating previous ovulation. Organ-specific antibodies to the adrenal cortex, ovarian theca cells, corpus luteum and testicular Leydig cells and non-organ-specific mitochondrial antibodies were detected by immunofluorescence.

Discussion

Autoimmune oophoritis is a rarely described condition, although its exact prevalence is unknown. It is characterized histologically by lymphocytic and plasma cell infiltration in relation to developing follicles. This leads to primary gonadal dysfunction which is characterized by elevated FSH and LH levels with a normal prolactin level (Scully *et al.* 1986; Coulam 1982). The histopathological features described in our patient are similar to those described by Gloor & Hurlimann (1984) and represent the second report in which both ovaries demonstrated lymphoplasmacytic infiltration of the developing ovarian follicles. The finding of autoantibodies to ovarian constituents has been reported in 15–40% of this follicular type of ovarian failure (Coulam 1982). Premature ovarian failure is associated with Addison's disease (Irvine 1974) and it is of interest that this patient had adrenal cortex antibodies.

It is important to consider the possibility of autoimmune oophoritis in women under the age of 35 who present with menopausal symptoms. Both Scully *et al.* (1986) and van der Merwe (1981) suggest that treatment with glucocorticoids in such patients will result in the restoration of menses but as our patient had been sterilized, fertility did not need to be restored. Recognition of the histopathological appearances in oophorectomy specimens should prompt further endocrine, antibody and HLA studies. Long-term surveillance is required as autoimmune oophoritis is associated with almost

St Thomas's Hospital, London SE1 7EH
C D A. WOLFE *Registrar in Obstetrics and Gynaecology*

Royal Army Medical College, Millbank, London SW1P 4RJ
R. W. STIRLING *Senior Lecturer in Pathology*

Correspondence: C. D. A. Wolfe

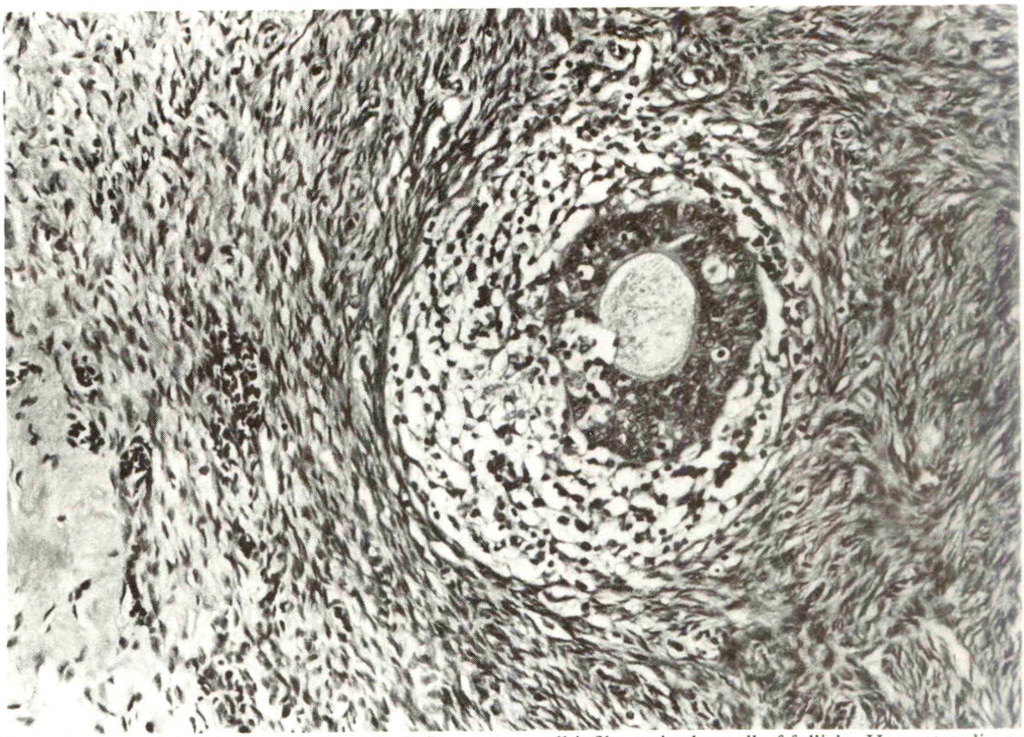

Fig. 1. Section of ovary demonstrating the inflammatory cell infiltrate in the wall of follicle. Haematoxylin and eosin. ×40.

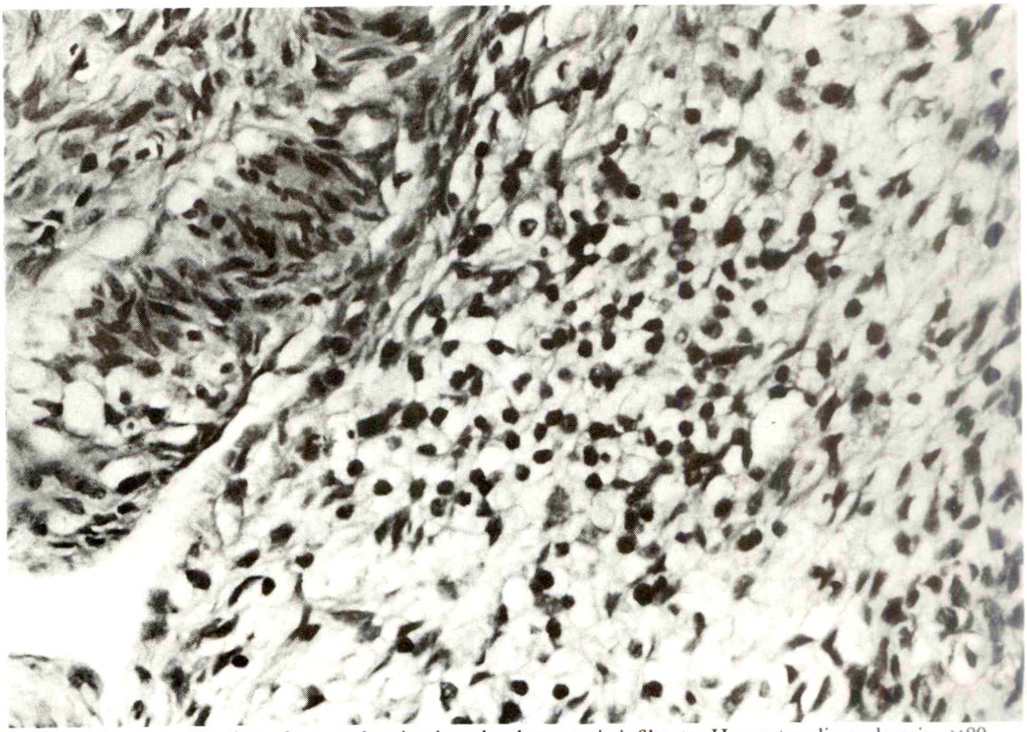

Fig. 2. Higher magnification of ovary showing lymphoplasmacytic infiltrate. Haematoxylin and eosin. ×80.

every autoimmune-mediated disease (Irvine 1974; Scully *et al.* 1986; van der Merwe 1981).

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References

Coulam, C. B. (1982) Premature gonadal failure. *Fertil Steril* **38**, 645-655.

Gloor, E. & Hurlimann, J. (1984) Autoimmune oophoritis. *Am J Clin Pathol* **81**, 105-109.

Irvine, W. J. (1974) Autoimmunity in endocrine disease. *Proc R Soc Med* **67**, 548-555.

Scully, R. E., Mark, E. & McNeely, B. U. (1986) Case records of the Massachusetts General Hospital. Case 46. *N Engl J Med* **315**, 1336-1343.

van der Merwe, J. V. (1981) Hypergonadotrophic amenorrhoea. *S Afr Med J* **59**, 42-46.

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SHORT COMMUNICATIONS

Extraction of a low molecular weight antibacterial peptide from human placenta

T. M. N. Scane *Research Assistant,* J. F. Guest *Post-Doctoral Research Associate* & D. F. Hawkins *Professor of Obstetric Therapeutics, Institute of Obstetrics and Gynaecology, Hammersmith Hospital, London*

The antibacterial activity of human amniotic fluid is widely documented (e.g. Hawkins & Scane 1983). The principal antibacterial components are β-lysin (Gusdon 1962; Ford *et al.* 1981) and a low molecular weight peptide (Schlievert *et al.* 1976; Scane & Hawkins 1984, 1986). This study sought to determine the distribution of the low molecular weight antibacterial component within the pregnant uterine cavity.

Methods

Placental and fetal membranes were obtained from patients who were delivered between 36 and 41 weeks gestation (mean 39·1, SD 1·8). All operations were performed at 0–4°C unless otherwise stated. Blood-free tissues were homogenized into phosphate-buffered saline (PBS) (9 ml/g, wet weight). Nuclear, mitochondrial and microsomal fractions were prepared by centrifugation at 1000, 15 000 and 100 000 *g* respectively, washed and stored at −20°C.

Subcellular fractions were lysed in 5 mmol/l Tris-HCl, pH 8·1, and together with the cell cytosol, were ultrafiltered, concentrated (Scane & Hawkins 1986) and resolved in 50 mmol/l ammonium acetate, pH 7·0, containing 10 μmol/l zinc chloride. Protein concentrations were assessed by the method of Lowry *et al.* (1951) with bovine serum albumin (Fraction V) as standard. Antibacterial activity was determined as described previously (Scane & Hawkins 1984, 1986).

Extracts were fractionated by high performance liquid chromatography (HPLC, Zorbax ODS 4·6 × 250 mm; Hawkins & Scane 1983), using methanol echelon elution. The fractions were dried and assayed for antibacterial activity. Polyacrylamide gel electrophoresis (PAGE) was performed as described by Swank & Munkres (1971), using a commercial staining procedure (Bio-Rad Silver Stain Kit). Gel lanes were excised, cut into 5-mm slices and destained. The activity of each slice was recovered by homogenization into acid alcohol.

Results

Antibacterial activity was observed in all homogenates of placental villous tissue (mean 1·3 units/g, SD 0·67) and recovered in acid alcohol extracts of their lyophilized ultrafiltrates (mean 0·73 units/g, SD 0·24). No activity was found in homogenates of either amnionic or chorionic membranes or their extracts.

Subcellular fractions prepared from placental villous tissue, all displayed antibacterial activity (Table 1). Most was found in the cytosolic and microsomal fractions. The microsomal fraction also expressed the greatest specific activity (c.f. amniotic fluid 2·7 units/mg protein, SD 1·2; Scane 1986). The gradients from antibacterial assays (de Louvois 1982) differed. Those of the cytosolic and nuclear fractions were steeper than those of the mitochondrial and microsomal fractions ($P<0·005$), but similar to that of the low molecular weight component found in amniotic fluid (7·6 mm/log unit, SD 0·55; Scane 1986).

Antibacterial activity of the cytosol and particulate fractions was resolved into two discrete fractions (6 and 7) by HPLC, which correspond to elution with 40% methanol. PAGE analysis revealed that one major and several minor peptides were present in these fractions. Activity, recovered from the gel lane bearing fraction 6, was found in that slice which contained the most abundant peptide, as determined by silver stain.

Correspondence: T. M. N. Scane, May & Baker Ltd, Dagenham, Essex

Table 1. Distribution of antibacterial activity through subcellular fractions of human placental homogenates

Fraction	Activity (units/g tissue) Mean (SD)	(%)	Specific activity (Units/mg protein)	Ratio	Slope of inhibition curve (mm/unit) Mean (SD)
Homogenate	5·08 (0·63)	(100)	0·19		
Cytosol	1·80 (0·40)	36	0·13	1·0	7·5 (0·32)
Nucleus	0·92 (0·19)	18	0·37	2·8	7·5 (0·75)
Mitochondria	0·77 (0·16)	15	0·52	4·0	5·7 (0·42)
Microsomes	1·79 (0·90)	35	4·33	33·3	5·7 (0·64)

Antibacterial activity expressed as a fraction of both tissue weight (units/g tissue) and the protein concentration of each subcellular fraction. Results are mean (SD) values of three samples.

No peptides were apparent in fractions 1, 2, 3, 4 or 8, while fraction 5 was highly heterogeneous.

Discussion

Antibacterial activity very similar to that expressed by human amniotic fluid (Scane & Hawkins 1984, 1986) was detected in all subcellular fractions of the human placental villous tissue but not in either amnionic or chorionic membranes. This low molecular weight component presumably protects the body of the placenta from microbial attack. The antibacterial component was present in very large quantities in the placental microsomal fraction. Therefore, this factor may be secreted into, and protect, the amniotic fluid space.

Acknowledgments

We are grateful to the labour ward staff at Hammersmith Hospital for the clinical specimens.

References

Ford, L. C., Kasha, W., Heins, Y., DeLange, R. J., Wright, J. D., Alexander, G. & Lebhertz, T. B. (1981) Identification of β-lysin as a zinc-dependant antibacterial protein in amniotic fluid. *J Obstet Gynaecol* **2**, 79-84.

Gusdon, J. (1962) A bactericidin for *Bacillus subtilis* in pregnancy. *J Immunol* **88**, 494-499.

Hawkins, D. F. & Scane, T. M. N. (1983) Polipeptidi e proprieta' antimicrobiche del liquido amniotico. In *Il Liquido Amniotico* (Vecchietti, G. & Di Renzo, G. C., eds), Piccin Editore, Italy, pp. 751-766.

de Louvois, J. (1982) Factors affecting the assay of antimicrobial drugs in clinical samples by the plate diffusion method. *J Antimicrob Chemother* **9**, 253-265.

Lowry, O. H., Rosebrough, N. J., Farr, A. L. & Randall, R. J. (1951) Protein measurement with the Folin-Phenol reagent. *J Biol Chem* **193**, 265-275.

Scane, T. M. N. (1986) An investigation into the pharmacologically-active fractions of amniotic fluid. PhD Thesis, University of London.

Scane, T. M. N. & Hawkins, D. F. (1984) Antibacterial activity in human amniotic fluid: relationship to zinc and phosphate. *Br J Obstet Gynaecol* **91**, 342-348.

Scane, T. M. N. & Hawkins, D. F. (1986) Antibacterial activity in human amniotic fluid: dependence on divalent cations. *Br J Obstet Gynaecol* **93**, 577-581.

Schlievert, P., Johnson, W. & Galask, R. P. (1976) Isolation of a low molecular weight antibacterial system from amniotic fluid. *Infect Immun* **14**, 1156-1166.

Swank, R. T. & Munkres, K. D. (1971) Molecular weight analysis of oligopeptides by electrophoresis in polyacrylamide gel with sodium dodecyl sulphate. *Anal Biochem* **39**, 462-477.

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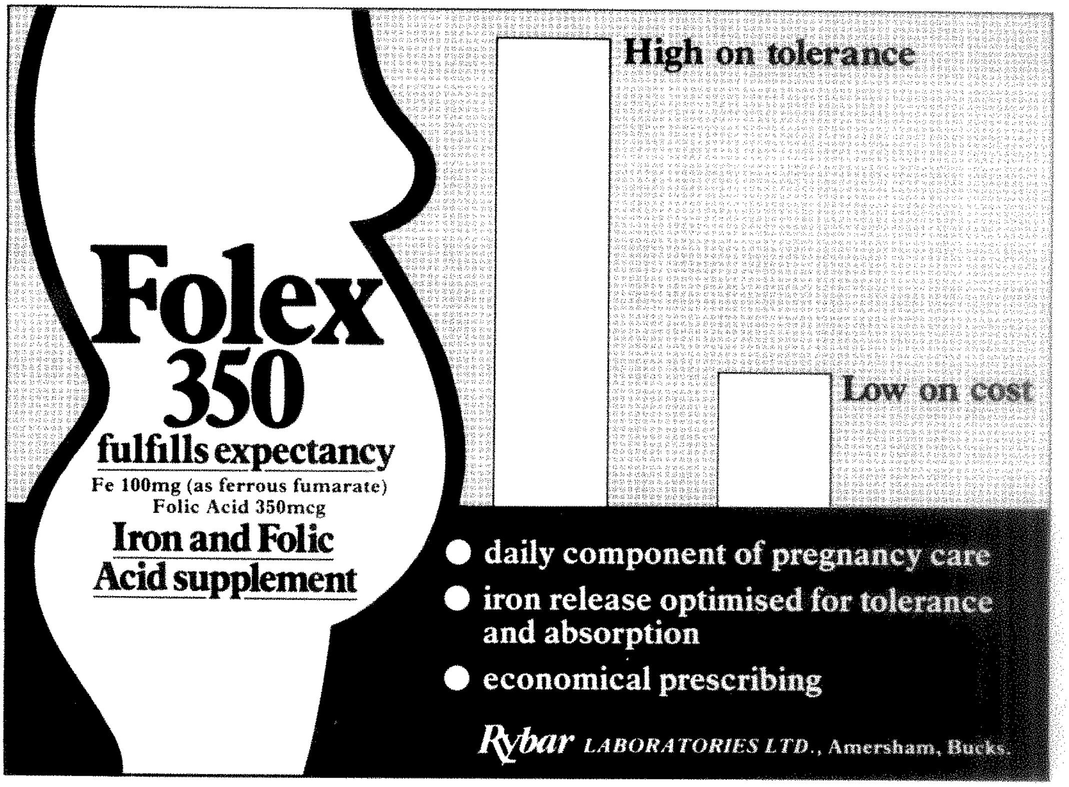

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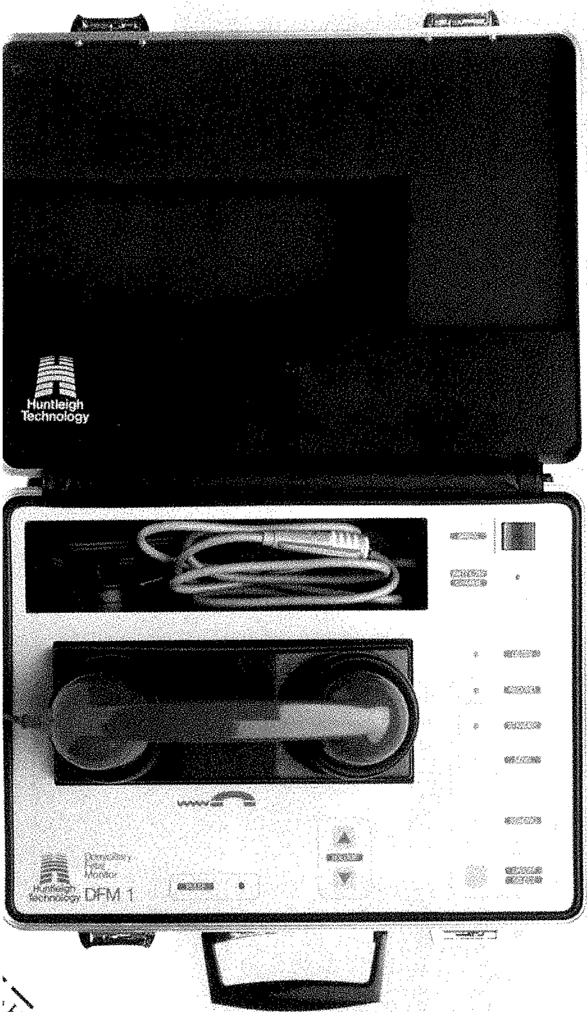

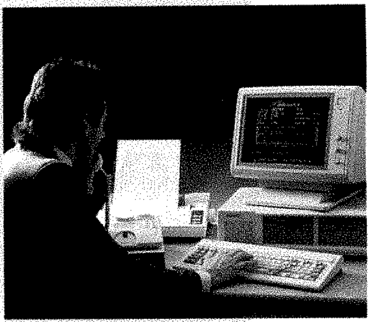

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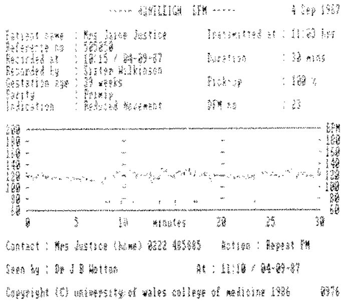

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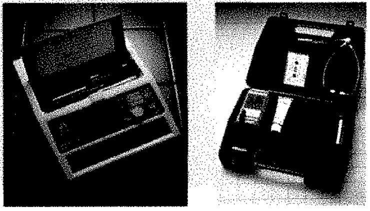

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British Journal of Obstetrics and Gynaecology
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CORRESPONDENCE

Magnetic resonance imaging (MRI) in obstetrics. II. Fetal anatomy

Dear Sir,

The paper by Powell *et al.* [*Br J Obstet Gynaecol* (1988) **95,** 38–46] sets out well the potential and limitations of conventional magnetic resonance imaging (MRI) in obstetrics with respect to fetal anatomy.

We agree with the authors' conclusion that the future mode of choice is likely to be based on the echo planar technique. This does, however, require specialist equipment and is not easily implemented on the current generation of MR equipment. We find there is greater potential and fewer limitations in the use of the fast-scan (or gradient echo) technique. We use a General Electric 1·5 T Signa System within the guidelines laid down by the National Radiological Protection Board (1983). By using short TR (repetition time) a single image can be obtained in 3–9 s. This allows a series of images in one axis to be obtained in 30–90 s, and images in all three axes in approximately 1·5–4·5 min. Subsequent diagnostic images from a specific region can then be obtained in a further 5 min.

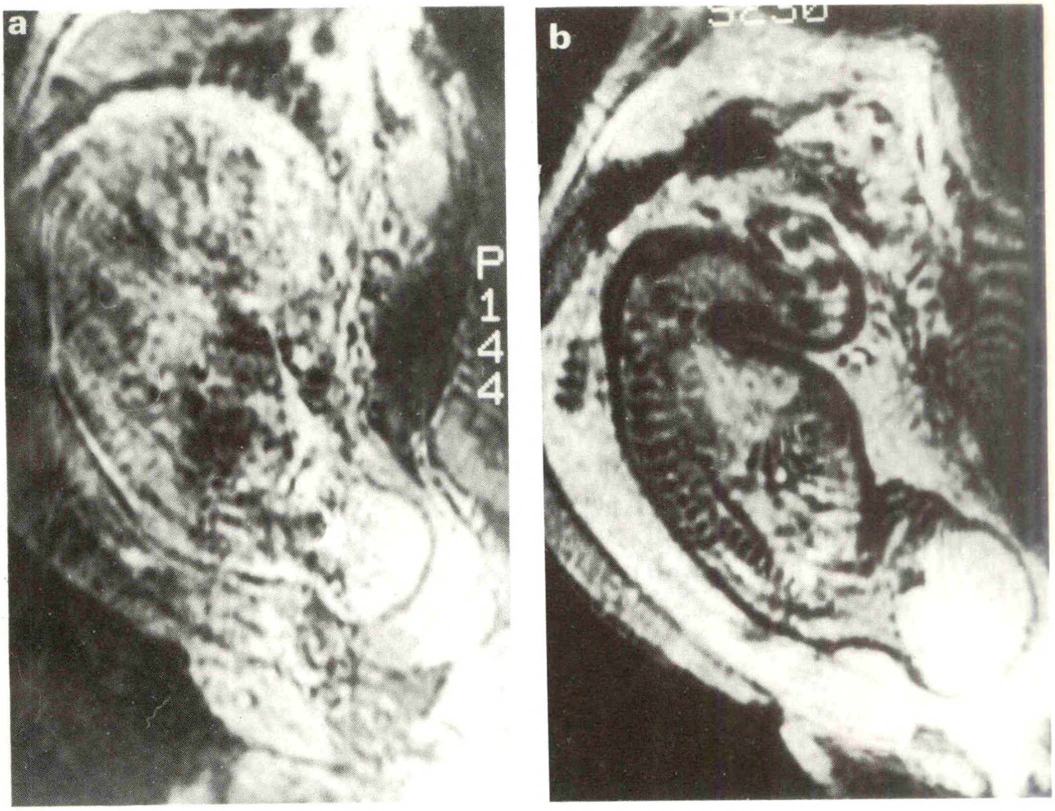

Fig. 1. Differences in image quality due to distortion from fetal movement. (a) Conventional spin-echo image. TR 2000 ms, TE 40. (b) Fast-scan technique. TR 25 ms, TE 12, flip angle 10.

The reduction in time has many advantages. It allows more studies to be done in a period of time and is more acceptable to the patient. The speed with which an image can be obtained allows for more accurate orientation. It is, therefore, possible to obtain images of different fetal parts by design rather than fortuitously. Most importantly, reduction in scanning time decreases the distortion due to movement. Image distortion occurs not only because of fetal movement, but also because of resultant movement in the protons in the amniotic fluid. The improvement in image quality can be seen in Fig. 1a and b. The use of the fast-scan technique minimizes image degradation and will allow greater application for MRI in fetal anatomy.

We are now working on applying three-dimensional fast-scan imaging techniques which will reduce imaging time even further.

Anne S. Garden
Senior Lecturer
Department of Obstetrics and Gynaecology
Richard Griffiths
Senior Lecturer
Department of Medicine
Michael Weindling
Senior Lecturer
Department of Child Health
Peter Martin
Lecturer in Magnetic Resonance
Magnetic Resonance Research Centre
University of Liverpool
Pembroke Place
Liverpool L69 3BX

References

National Radiological Protection Board (1983) Revised guidance on acceptable limits of exposure during nuclear magnetic resonance clinical imaging. *Br J Radiol* **56,** 974-977.

Powell, M. C., Worthington, B. S., Buckley, J. M. & Symonds, E. M. (1988) Magnetic resonance imaging (MRI) in obstetrics. II. Fetal anatomy. *Br J Obstet Gynaecol* **95,** 38-46.

Is treatment needed for mild impairment of glucose tolerance in pregnancy? A randomized controlled trial

Dear Sir,

Dr Li and colleagues [*Br J Obstet Gynaecol* (1987) **94,** 851–854] are to be congratulated on confronting this question. There is certainly a feeling that excessive treatment of this biochemical abnormality is unjustified, and Persson *et al.* (1985) reported no advantage to giving insulin and diet, over diet alone in the group of women whose 1-h postprandial plasma glucose level was less than 9 mmol/l.

The design of study reported by Li *et al.* leaves much to be desired. The use of alternate allocation instead of randomization is open to abuse, and the exclusion of 51 patients, many of whom 'were not managed according to the protocol by individual consultants', seems to highlight this. In the impaired glucose tolerance (IGT) group, only 59 of 98 were entered.

The major problem with the study is the absence of suitable end points. Although women in the 'treatment group' had blood sugar profiles recorded, there is no information about the results or what action was to be taken if the glucose levels were abnormal. We are unable to compare glucose levels in the control group as these were not measured. Without this information it is impossible to see whether the diet chosen had any therapeutic effect on mean plasma glucose.

The end point which is surely of most relevance to the management of disordered glucose tolerance in the woman, is the development of fetal hyperinsulinism. This can be assessed from amniotic fluid insulin levels in late pregnancy (Weiss *et al.* 1986), or by measuring cord blood insulin or C-peptide levels. Li *et al.* do report an absence of neonatal hypoglycaemia in both groups, but do not comment on treatment of the newborn.

An indirect measurement of fetal hyperinsulinism is excessive birthweight. In the series reported by Li *et al.* of women with IGT, 24% of the control group gave birth to babies weighing >90th centile of weight for gestational age, against 13% in the treated group. Four of 29 women in the control group but none of the 30 women in the treated group had babies >4 kg. I would not agree with their reassuring conclusion that these differences 'probably have no clinical significance'.

Robert Fraser
Senior Lecturer
Department of Obstetrics and Gynaecology
Clinical Sciences Centre
Northern General Hospital
Herries Road
Sheffield S5 7AU

References

Li, D. F H., Wong, V. C. W., O'Hoy, K. M. K. Y., Yeung, C. Y. & Ma, H. K. (1987) Is treatment needed for mild impairment of glucose tolerance in pregnancy? A randomized controlled trial *Br J Obstet Gynaecol* **94**, 851-854.

Persson, B., Stangenberg, M., Hansson, U. & Norlander, E. (1985) Gestational diabetes mellitus (GDM). Comparative evaluation of two treatment regimens, diet versus insulin and diet *Diabetes* **34 (Suppl. 2)**, 101-105.

Weiss, P A. M., Hofmann, H M , Winter, R. R , Lichtenegger, W., Purstner, P. & Haas, J. (1986) Diagnosis and treatment of gestational diabetes according to amniotic fluid insulin levels. *Arch Gynecol* **239**, 81-91.

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BOOK REVIEWS

Principles of Gynaecological Surgery edited by Stuart Stanton. Springer-Verlag, London, 1987, 306 pages with figures and tables, £29.50

This book is designed to complement, not to replace, current textbooks of gynaecological surgery, an intention stated in the introduction, though less evident in the title.

It contains a vast amount of information that might be acquired through observation, precept and anecdote during apprenticeship to an experienced gynaecological surgeon though a few chapters are more specialized. Some chapters are comprehensive, some very selective and a few have long paragraphs of surprising simplicity that might give cause to question at what point in the doctor's career it should be read.

Much of the material, for example in the management of unexpected laparotomy findings, urinary and intestinal injuries, could form the basis of numerous MRCOG questions, written and viva, when the competence to do unassisted surgery is being tested.

This is an easy book to read and is well presented and illustrated. All registrars should read it and indeed gynaecologists at any stage could do so with profit.

It is not a reference book but primarily one for the departmental library.

W. T. Fullerton

Prenatal Ultrasound: A Color Atlas with Anatomic and Pathologic Correlation by Beverly A. Spirt, Lawrence P. Gordon & Michael Oliphant. Churchill Livingstone, Edinburgh, 1987, 148 pages with figures and tables, £49.50

One might imagine that the subject of prenatal diagnosis of fetal malformation does not readily lend itself to the form of the coffee-table book, but this is not necessarily so. This is a rather large and lavishly illustrated volume, compiled over several years, which has emerged from a good idea—to juxtapose ultrasonic images of the fetus with photographs of pathological and anatomical preparations and other relevant material, including X-rays. The first section of the book deals with normal fetal anatomy and rightly emphasizes the changing appearances that occur with advancing gestation. The second, and larger, section deals with malformation, system by system and condition by condition, listing diagnostic criteria and brief details about aetiology and associated conditions, as well as illustrations of the defect. There are gaps, congenital heart disease for one. There are also flaws—the quality of some of the ultrasonograms is poor (and this is not confined to those malformations which are difficult to reproduce or which are so rare that the illustrations are likely to be old) and the cited references are offensively parochial.

The book has been written from the standpoint of the radiologist and not the obstetrician and the authors carefully sidestep the complexities of management. Which malformations justify fetal blood sampling for karyotyping, and which do not? Which malformations have such a poor prognosis that termination of pregnancy is justified, and which do not? Some of the many spaces in the book could be usefully employed for such additional information. The ultrasonic images are, throughout, black on white which is a constant irritant to the British reader. Can these not be easily reversed by the publisher?

This is not an inexpensive book and it is one that needs to be improved to justify its cost.

J. P. Neilson

Prematurity edited by V. Y. H. Yu & E. Carl Wood. Churchill Livingstone, Edinburgh, 1987, 292 pages with figures and tables, £30.00

Although the ability to care for the sick preterm infant has existed for 3 decades, it is only in the last 10 years that intensive care for the tiniest baby has been more than experimental. So rapidly has information accumulated that much recent work is only available in the journals. Books about the premature derive most of their material from studies of infants of between 32 and 37 weeks gestation, while the problems at the 'cutting edge' of neonatology are mainly to do with infants of less than 32 weeks.

Melbourne, Australia, has in recent years been the source of a stream of obstetric and neonatal paediatric research, and Professors Yu and Wood have therefore been able to produce this up-to-date book in the minimum time by using all local talent.

The 14 chapters are evenly divided between obstetrics and neonatology, but aim to be reviews of the most recent developments rather than form a comprehensive textbook. The first four chapters cover the epidemiology, physiology, prediction and prevention of preterm birth, and are concise, up-to-date and well-referenced reviews. These are followed by two straightforward chapters on obstetrical management and anaesthesia for preterm delivery.

Cardiorespiratory development and adaptation is well covered, and although much of this is rabbit and sheep physiology (this is an Australian book), there are plenty of human data as well. A rather brief review of neonatal complications is followed by chapters on specific problems such as surfactant deficiency, periventricular haemorrhage and ischaemia, and neurodevelopmental outcome. The latter two chapters rely heavily on Melbourne data. Psychological aspects are covered in a chapter which reviews similar ground to Klaus and Kennell, and tells us that most (Australian) mothers think their prems look like rabbits. Ethical issues are dealt with by discussion of a particular ethicist's viewpoint rather than as a review, and the book ends with a bit of crystal ball-gazing from Professor Wood.

I very much enjoyed reading this book and would recommend it strongly to anyone concerned with preterm pregnancy and birth as a highly readable update.

R. Cooke

Common Problems in Obstetric Anesthesia
edited by Sanjay Datta & Gerard W. Ostheimer.
Year Book Medical Publishers, Inc., Chicago, London, 1986, 496 pages with figures and tables, £38.50

As the market for conventional texts in obstetric anaesthesia progresses towards saturation point it is refreshing to see a volume which is, according to the preface, not a typical textbook. The editors, who are both associate professors in anaesthesia at Harvard and the Brigham and Women's Hospital, Boston, have assembled a collection of problem-orientated management profiles and discussions, each introduced by a 'case presentation'. The 29 chapters have up to six subchapters written by different individual or paired authors including a nurse, a psychologist, obstetricians, perinatologists, neonatologists and a preponderance of anaesthetists. The concept may have much to commend it but problems with presentation are soon evident. The first chapter, 'Physiology of Pregnancy', begins encouragingly enough with a concise description of relevant cardiovascular and respiratory changes in late pregnancy, in response to the hypothetical presentation of a 23-year-old primigravida at 39 weeks gestation for pre-anaesthetic assessment and consultation. Why she needed this attention we are not told. Could it be routine in the author's hospital? The chapter ends with a piece which explains briefly why pregnant patients are at risk of aspiration during anaesthesia then describes, at greater length, the prophylaxis, pathophysiology, diagnosis and treatment of aspiration of gastric contents. The very next chapter is devoted to prevention and management of acid aspiration with two subchapters, both headed 'Aspiration in Obstetrics' and introduced by the same case presentation. The repetition of concurring views is tedious but there are other subjects, such as preterm labour, anaesthesia for pregnant diabetics and breech presentation where separate contributions from obstetricians and anaesthetists provide balanced views of contentious issues. In some instances, for example, the anaesthetist's view of utero-placental circulation, the specific details of the introductory case presentation are irrelevant or ignored. One of the 'cases' is represented as a candidate in an American board examination who is asked to talk about placental transfer of drugs and disposition in the fetus/newborn. Clinicians expecting to learn from the portrayal of practical clinical problems may not be impressed by reference to drugs as 'xenobiotic compounds' or the assertion that 'An intelligent discussion of basic perinatal pharmacology involves the construction of a pharmacologic model (in this situation the maternal–placental–fetal unit), a description of the pharmacokinetic principles of the model, and finally a pharmacodynamic overview of drug–model interactions'. This is definitely not a typical textbook and although it may fill a gap in the market it is less likely to achieve popularity in the UK than in the USA. It is also less likely to appeal to obstetricians than anaesthetists and cannot be recommended as an essential addition to the manuals which ordinary maternity units should have in their labour ward or departmental libraries.

R. P. Husemeyer

Books received some of which may be reviewed at a later date

The Status of the Human Embryo edited by G. R. Dunstan & M. J. Sellars. Oxford University Press/King Edward's Hospital Fund for London, 1988, 119 pages, £15.50

Obstetric Fistula by Robert F. Zacharin. Springer-Verlag, Wien, New York, 1988, 286 pages illustrated, DM 230

Atlas of Fetal Skeletal Radiology by Asher Ornoy, Zvi Borochowitz, Ralph Lachman & David L. Rimoin. Year Book Medical Publishers, Inc., Chicago, London, 1988, 147 pages fully illustrated, £61.00

The Year Book of Urology 1987 edited by Jay Y. Gillenwater & Stuart S. Howards. Year Book Medical Publishers, Inc., Chicago, London, 340 pages with figures and tables, £35.50

Diagnostic Picture Tests in General Medicine by Michael Zatouroff. Wolfe Medical Publications Ltd, Ipswich, 1988, 128 pages fully illustrated with colour plates, £6.50

Preparing for Pregnancy by Philip J Robarts. Faber & Faber, London, 1988, 84 pages illustrated, £2.95

The Obstetric Forceps A Short History and Descriptive Catalogue of the Forceps in the Museum of the Royal College of Obstetricians and Gynaecologists by Bryan M. Hibbard. Copies may be obtained from The Royal College of Obstetricians and Gynaecologists, 27 Sussex Place, Regent's Park, London NW1 4RG, £2.00

Gynecologic Surgery Under Local Anesthesia by A. Jefferson Penfield. Urban & Schwarzenberg, Baltimore, Munich, 1986, 197 pages, £29.75

Cytological Screening in the Control of Cervical Cancer: Technical Guidelines World Health Organization, Geneva, 1988, 52 pages, Sw.fr.11

An 'Epidemic' of Adolescent Pregnancy?: Some Historical and Policy Considerations by Maris A. Vinovskis. Oxford University Press, 1988, 284 pages, £22.50

What Every Woman Needs to Know: Facts and Fears About Pregnancy, Childbirth and Womanhood edited by Penny Junor. Century Paperbacks, London, 1988, 203 pages, £5.95

Directions to contributors

All papers should be sent to The Editor, *British Journal of Obstetrics and Gynaecology*, 27 Sussex Place, Regent's Park, London NW1 4RG. Papers received are assumed to have been submitted exclusively to the *British Journal of Obstetrics and Gynaecology* and *all* authors must give signed consent to publication in a letter sent with the manuscript. The Editor will decide on the time of publication and retains the usual right to modify the style and length of a contribution; major changes will be agreed with the author(s).

Presentation of manuscripts

Two copies of the manuscript and illustrations should be sent Manuscripts should be typed double spaced on one side of the paper, with wide margins. The names of author(s) and their appointment(s) and addresses at the time of preparation of the manuscript should be given. Authors are advised to keep a copy of all manuscripts, as no responsibility can be accepted for loss

Reports of original work should usually be arranged in the conventional order of summary, introduction, methods, results, discussion, acknowledgments and references, with suitable headings for each part. Two further sub-divisions, with appropriately less significant headings, can be used; the third order heading runs on with text at a paragraph opening Results may be presented in the text, in tables and/or figures, the text should, in general, comment on rather than repeat tion in tables. The summary should contain a factual the methods and results in not more than 150 . than a description of the subject of the paper and s of the author(s).

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Units and abbreviations

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Drugs are described by their official names but trade names should be indicated in brackets the first time a drug is quoted in the main text.

Statistics

Authors should describe clearly the design of their investigation and the source of the data. All statistical methods should be specified so that it is clear which was used where. Papers omitting this information may be returned without review. The basic principle to follow is to supply sufficient information about the design and methods of analysis to allow the research to be repeated by someone else

Some points of detail to note are:

(1) It is not acceptable to present the results of a statistical analysis solely by a *P* value—actual results such as means or proportions should always be given, along with the test statistic

(2) The use of confidence intervals is encouraged

(3) The symbol ± should not be used when presenting SE or SD. Presentation such as 'the mean was 14·2 (SD 3·2) mg' is preferred

(4) When paired comparisons are made it is desirable to indicate the variability of within-pair differences

(5) Unusual methods of analysis should be described and/or referenced.

Authors are referred to the general statistical guidelines of Altman *et al* (1983) for advice about the presentation and interpretation of the statistical aspects of their research

Altman, D G , Gore, S M., Gardner, M J & Pocock, S. J. (1983) Statistical guidelines for contributors to medical journals. *Br Med J* **286**, 1489–1493.

Human experiments

Manuscripts should contain a statement that the work was approved by the ethics committee of the institution in which it was done and that subjects gave informed consent to the work The editors reserve the right to reject papers if they consider the ethical justification to be questionable.

References

In the text, use the name of the author(s) followed by their date of publication, where there are two authors use the form· Smith & Brown 1972, where there are more than two authors use Robinson *et al.* 1979

Arrange the list of authors quoted at the end of the text in alphabetical order set out as follows:

Name(s) and initials of all author(s), year of publication (in brackets), title of the article, name of the journal (abbreviated according to *Index Medicus*), volume number, first and last page numbers. In the case of books the order is· Name(s) and initials of author(s), year of publication (in brackets), full title, edition, publisher and place of publisher, page numbers Where appropriate, the chapter title and the names of the editors should be given.

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Trudinger, B J , Lewis, P J & Petit, B (1979) Fetal breathing in intrauterine growth retardation. *Br J Obstet Gynaecol* **86**, 432-436.

Hytten, F E & Leitch, I (1971) *The Physiology of Human Pregnancy* 2nd edn, Blackwell Scientific Publications, Oxford, p. 26

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